

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 45/06, 31/57, A61P 15/18 // (A61K 31/57, 31:535, 31:565) (A61K 31/57, 31:495, 31:565) (A61K 31/57, 31:47, 31:565)		A1	(11) International Publication Number: WO 00/66165 (43) International Publication Date: 9 November 2000 (09.11.00)
<p>(21) International Application Number: PCT/US00/11644</p> <p>(22) International Filing Date: 1 May 2000 (01.05.00)</p> <p>(30) Priority Data: 09/305,003 4 May 1999 (04.05.99) US 09/552,357 19 April 2000 (19.04.00) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/552,357 (CON) Filed on 19 April 2000 (19.04.00)</p> <p>(71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Girardia Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San</p>		<p>Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). MARSCHKE, Keith, B. [US/US]; 12565 Escala Drive, San Diego, CA 92128 (US). TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US).</p> <p>(74) Agents: KODROFF, Cathy, A. et al.; Howson & Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
(54) Title: CONTRACEPTIVE COMPOSITIONS CONTAINING QUINAZOLINONE AND BENZOXAZINE DERIVATIVES			
<p style="text-align: center;">(I)</p>			
<p>(57) Abstract</p> <p>This invention relates to cyclic combination therapies utilizing, in combination with progestins, estrogens, or both, compounds which are progesterone receptor antagonists of general structure: (I) wherein: R¹ and R² are H, COR^A, or NR^BCOR^A, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heterocyclic; or R¹ and R² fuse to form 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic rings; R^A is H or optionally substituted alkyl, aryl, alkoxy, or aminoalkyl groups; R^B is H or alkyl; R³ is H, OH, NH₂, COR^C or alkyl, alkenyl, or alkynyl; R^C is H, alkyl, aryl, alkoxy, or aminoalkyl; R⁴ is H, halogen, CN, NO₂, alkyl, alkynyl, alkoxy, amino or aminoalkyl; R⁵ is benzene or 5- or 6-membered heterocyclic ring; R⁶ is H or alkyl; G₁ is O, NR₇, or CR₇R₈; G₂ is CO or CR₇R₈; provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈; R₇ and R₈ are H or an optionally substituted alkyl, aryl, or heterocyclic moiety; or pharmaceutically acceptable salt thereof. These methods may be used for contraception or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	S1	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NR	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CONTRACEPTIVE COMPOSITIONS CONTAINING QUINAZOLINONE AND BENZOXAZINE DERIVATIVES

Field of the Invention

5 This invention relates to regimens of administering compounds which are antagonists of the progesterone receptor in combination with a progestin, an estrogen, or both.

Background of the Invention

Intracellular receptors (IR) form a class of structurally related gene regulators 10 known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

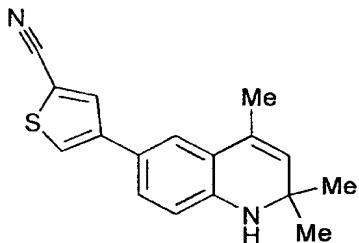
The natural hormone, or ligand, for the PR is the steroid progesterone, but 15 synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates 20 the production of mRNA and protein encoded by that gene.

A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist. PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in 25 the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus that can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces or ablates that risk.

- 2 -

PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 July 4, 1996). PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991). PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136). PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N.Y. Acad. Sci.*, **761**, 224, 1995).

Jones, et al, (U.S. Patent No. 5,688,810) describe the PR antagonist dihydroquinoline **1**.

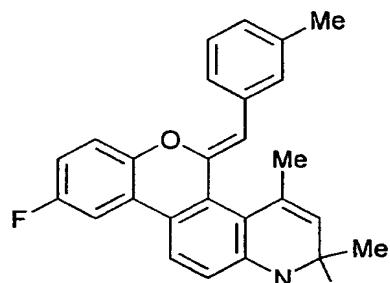


1

20

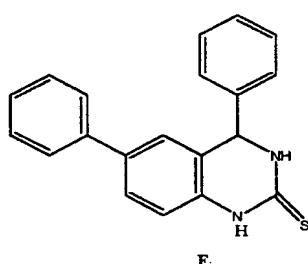
Jones, et al, described the enol ether **2** (U.S. Patent No. 5,693,646) as a PR ligand.

- 3 -



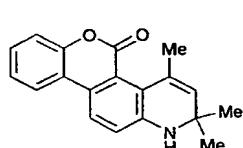
2

Jones, *et al.*, described compound 3 (U.S. Patent No. 5,696,127) as a PR
5 ligand.

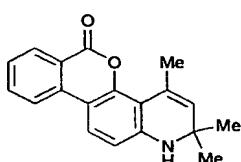


3

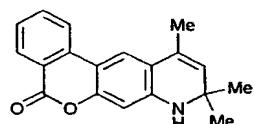
Zhi, *et al.*, described lactones 4, 5 and 6 as PR antagonists (J. Med. Chem., 41,
10 291, 1998).



4



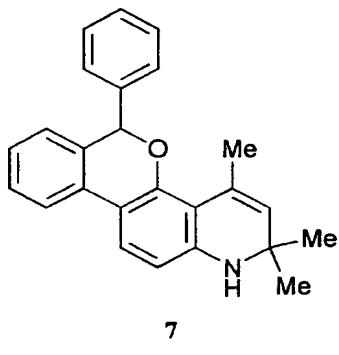
5



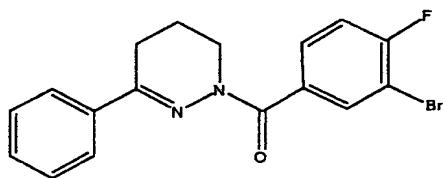
6

- 4 -

Zhi, et al., described the ether **7** as a PR antagonist (*J. Med. Chem.*, **41**, 291, 1998).

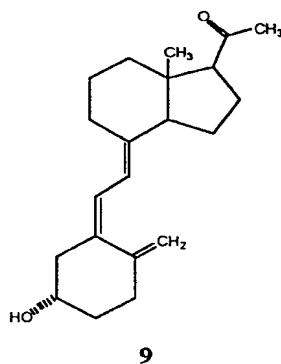


5 Combs, et al., disclosed the amide **8** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



8

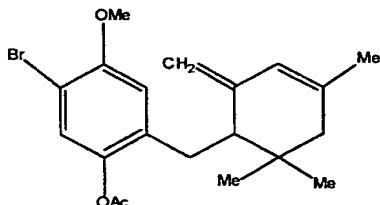
10 Perlman, et. al., described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



9

- 5 -

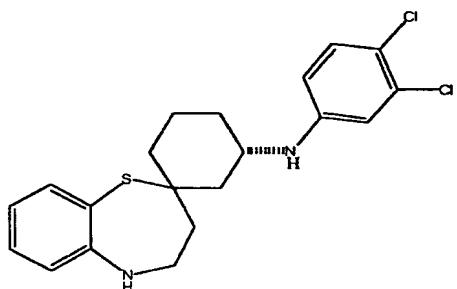
Hamann, *et al.*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



10

5

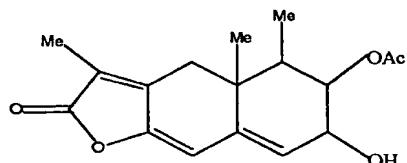
Chen, *et al.*, described the PR antagonist **11** (Chen, *et al.*, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



11

10

Kurihara, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).



12

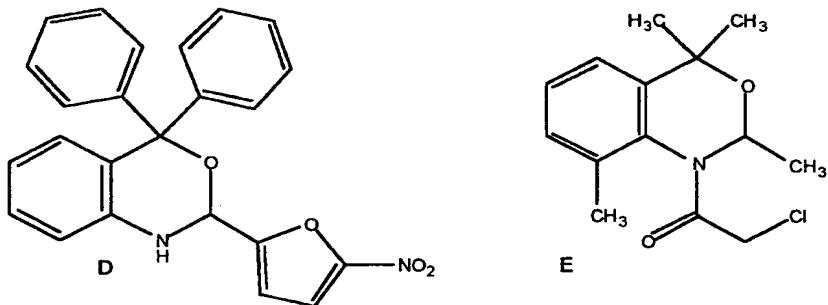
- 6 -

A number of publications reported the synthesis and utilities of benzodiazinones and benzoxazines. Included in this literature is the patent by Kubla et al. (US 4666913) which claimed that the compound such as **A** and **B** could be used as cardiotonic agents. Ning et al. reported the synthesis of quinazolinones such as **C**.

5

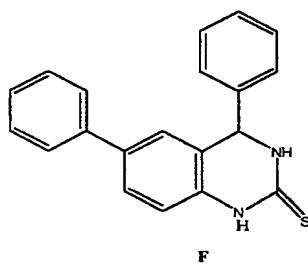
Gromachevskaya et al. (Chem. Heterocycl. Compd. (N.Y.), 33(10), 1209-1214 (1998)) studied the bromination process of certain benzoxazines such as compound **D**. Kobzina et al. (U.S. Patent No. 3,917,592) claimed that compounds such as **E** can be used as a herbicidal agent.

10



Pfleger et al. (Pharmazie, 37(10), 714-717(1982)) disclosed quinazolin-2-thiones such as compound **F** in their study of polarography of heterocyclics. No 15 activity of the compound **F** was mentioned.

15



U.S Patent No. 5,521,166 (Grubb) teaches cyclophasic hormonal regimens comprising an antiprogestin and a progestin wherein the progestin is administered in the alternating presence and absence of an antiprogestin. The disclosed regimens also provide for use of an estrogen for a period of from 2-4 days to prevent breakthrough bleeding.

5

Description of the Invention

This invention provides combination therapies and dosing regimens utilizing antiprogestational agents in combination with one or more progestational agents. This
10 invention further provides methods of treatment and dosing regimens further utilizing in combination with these antiprogestins and progestins, an estrogen, such as ethinyl estradiol.

These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea,
15 dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases described above includes the continuous administration or periodic discontinuation of
20 administration of the invention to allow for minimization of effect dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried
25 out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14-24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 µg to about

150 µg levonorgestrel per day, preferably equal in activity to from about 35 µg to about 100 µg levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be
5 administered at a dose of from about 2µg to about 50 µg per day and the estrogen may be administered at a dose of from about 10 µg to about 35 µg per day. In an oral administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention
10 may be administered alone or in combination with estrogen for the initial 18 to 21 days of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

15 Progestational agents useful with this invention include, but are not limited to, levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate . Among the preferred progestins for use in the combinations of this invention are levonorgestrel,
20 gestodene and trimegestone.

Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 µg of levonorgestrel. An antiprogestin compound of this invention may then be administered
25 at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of 5 from about 10 to about 35 µg. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, 10 preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 µg levonorgestrel, and an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 µg. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) 15 and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 µg. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

This invention also kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral administration over a 28-day cycle, preferably for one oral administration per day, 20 and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

25 a) an initial phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 µg levonorgestrel;

- 10 -

- b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
5 c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogestin, progestin or estrogen is administered.

A preferred embodiment of this kit may comprise:

- 10 a) an initial phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 µg levonorgestrel;
b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
15 c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

- 20 a) a first phase of from 18 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and
25 c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal

- 11 -

in activity to from about 35 to about 100 µg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

5 c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

10 a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg;

15 b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

20 a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg;

25 b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

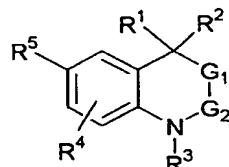
- 12 -

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase
5 followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

10 In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

15 These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units which are administered over the course of each day of the cycle contemplated.

20 Compounds of this invention which may be used as the anti-progestational agents in the kits, methods and regimens herein are those of the Formula I:



I

wherein:

R¹, R² are independent substituents selected from the group which includes H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or 5 NR^BCOR^A;

or R¹ and R² are fused to form:

- a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring;
- b) an optionally substituted 3 to 8 membered spirocyclic alkenyl; or
- c) an optionally substituted 3 to 8 membered heterocyclic ring

10 containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings of a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

15 R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl,

R^B is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl,

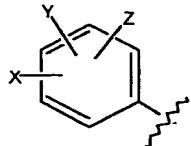
R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C,

20 R^C is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl,

25 R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, alkynyl, or substituted alkynyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl,

R⁵ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,

- 14 -



X is taken from the group including halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, alkynyl, or substituted alkynyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, amino, aminoalkyl, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

or

R^F is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR^G and containing one or two independent substituents from the group including H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^G is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R^G is H or C₁ to C₃ alkyl;

G₁ is O, NR₇, or CR₇R₈;

G₂ is CO or CR₇R₈;

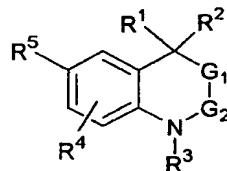
- 15 -

provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

R₇ and R₈ are independent substituents selected from H or an optionally substituted alkyl, aryl, or heterocyclic moiety;

5 or pharmaceutically acceptable salt thereof.

Preferred antiprogestin compounds of this invention include those of Formula I:



I

10 wherein:

R¹ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

15 R² is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₈ alkenyl, substituted C₂ to C₆ alkenyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;
or

20 R¹ and R² are fused to form an optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic ring containing one to three heteroatoms from the group including O, S and N, as described above;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl,

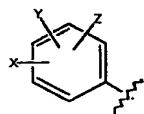
- 16 -

R^3 is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R^4 is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl,

10 R^5 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



15 X is selected from halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

20 R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

 R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

 Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

25 or

 R⁵ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁶ and containing one or two independent substituents

- 17 -

from the group including H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, C₁ to C₃ alkoxy;

R⁶ is H, or C₁ to C₃ alkyl.

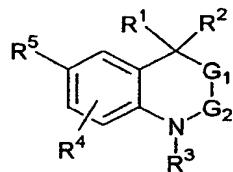
G₁ is O, NR₇, or CR₇R₈

5 G₂ is CO or CR₇R₈, with the proviso that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

wherein R₇ and R₈ are independent substituent selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic or a pharmaceutically acceptable salt thereof.

10

Still, more preferred antiprogestin compounds include those of the formula:



wherein:

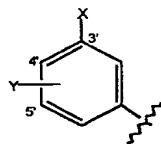
15 R¹ = R² and are selected from C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, or spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 6 membered spirocyclic ring;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, -COH, -CO(C₁ to C₄ alkyl) or -CO(C₁ to C₄ alkoxy);

20 R⁴ is H, halogen, NO₂, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl,

R⁵ is a disubstituted benzene ring containing the substituents X, and Y as shown below

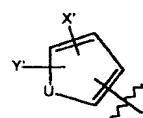
- 18 -



X is taken from the group including halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, C₁ to C₃ thioalkoxy,

5 Y is a substituent on the 4' or 5' position from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, C₁ to C₃ thioalkoxy
or

R⁵ is a five membered ring with the structure shown below



10

U is O, S, or NR⁶,

R⁶ is H, or C₁ to C₃ alkyl, C₁ to C₄ CO₂alkyl,

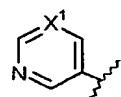
X' is from the group including halogen, CN, NO₂, C₁ to C₃ alkyl and C₁ to C₃ alkoxy

15

Y' is from the group including H and C₁ to C₄ alkyl

or

R⁵ is a six membered ring with the structure shown



20

X¹ is N or CX²,

X² is halogen, CN, alkoxy, or NO₂,

G₁ is O, NR₇, or CR₇R₈

- 19 -

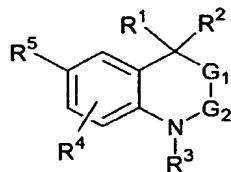
G_2 is CO or CR_7R_8

provided that when G_1 is O, G_2 is CR_7R_8 , and G_1 and G_2 cannot both be CR_7R_8 ;

wherein R_7 and R_8 are independent substituents selected from H, alkyl, 5 substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic;

or pharmaceutically acceptable salt thereof

Still, other preferred antiprogestin compounds are those of Formula I



I

10 wherein:

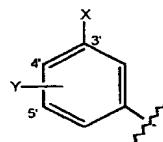
$R^1 = R^2$ and are selected from the group which includes CH_3 and spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 6 membered spirocyclic ring,

R^3 is H, OH, NH_2 , CH_3 , substituted methyl, COR^C ,

R^C is H, C_1 to C_3 alkyl, C_1 to C_4 alkoxy,

15 R^4 is H, halogen, C_1 to C_3 alkyl,

R^5 is a disubstituted benzene ring containing the substituents X, and Y as shown below



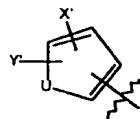
X is taken from the group including halogen, CN, methoxy, NO_2 , 2-thiazole,

20 Y is a substituent on the 4' or 5' position from the group including H and F,

or

R^5 is a five membered ring with the structure shown below

- 20 -



U is O, S, or NH,

X' is from the group including halogen, CN, NO₂,

Y' is from the group including H and C₁ to C₄ alkyl

5 G₁ is O, NR₇, or CR₇R₈

G₂ is CO or CR₇R₈

provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

10 R₇ and R₈ are independent substituent selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic; and pharmaceutically acceptable salts thereof.

The antiprogestin compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While 15 shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. It will be understood by one skilled in the art that the number of substituents listed for spirocyclic or 20 heterospirocyclic rings formed by fusing R₁ and R₂ will be determined by the size of the spirocyclic ring.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having one to eight carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one 25 carbon-carbon double bond and two to eight carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond and two to eight carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, 5 alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one 10 part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one to four 15 substituents from the group including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

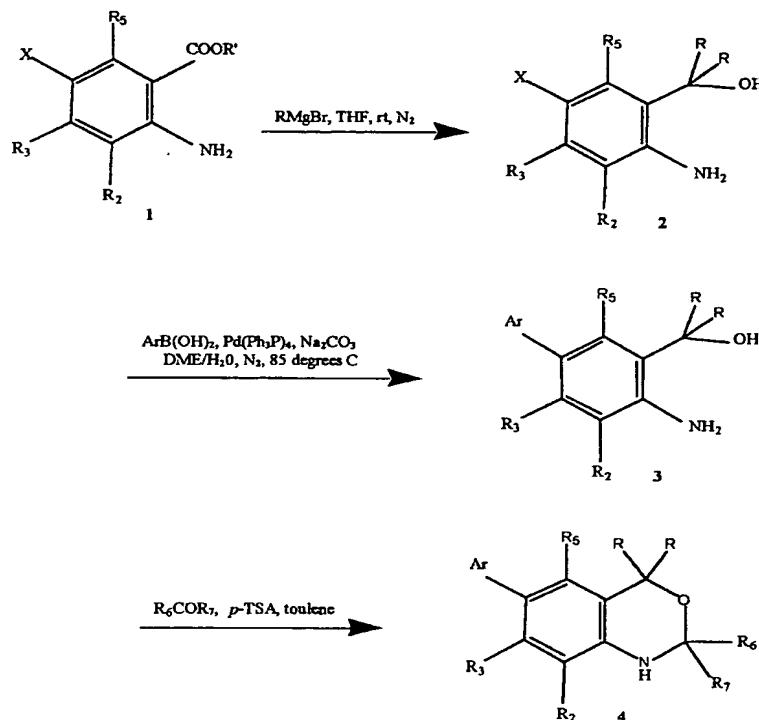
The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four 20 heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, 25 piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one to four substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, 5 alkylamino, or arylthio. The term "alkoxy" refers to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to indicate the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" refers to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" refers to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary 10 and tertiary amines wherein the alkyl or substituted alkyl groups, containing one to eight carbon atoms, which may be either same or different and the point of attachment is on the nitrogen atom. The term "halogen" refers to Cl, Br, F, and I element.

The antiprogestin compounds of this invention can be prepared following the Schemes illustrated below:

- 23 -

Scheme I



As demonstrated in Scheme I, the anti-progestational compounds of this invention are generally prepared by employing the suitable coupling reaction as a key step. An appropriately substituted ortho-amino benzoic acid or its derivatives such as ethyl ester ($\text{X} = \text{Br}, \text{I}, \text{Cl}$, or a latent coupling precursor such as alkoxy group which can be converted into OTf group suitable in the coupling reaction.) was treated with a suitable organo metallic reagent, e.g. Grignard reagent, in appropriate nonprotic solvents which include but not limited to THF or ether to give ortho-amino carbinol **2** under an inert atmosphere such as argon or nitrogen at -78°C to room temperature. The arylation of amino carbinol **2** to yield **3** can be effected by various coupling reactions including Suzuki, Stille reactions. These reactions are commonly performed in the presence of a transition metallic catalyst, e.g., palladium or nickel complex often

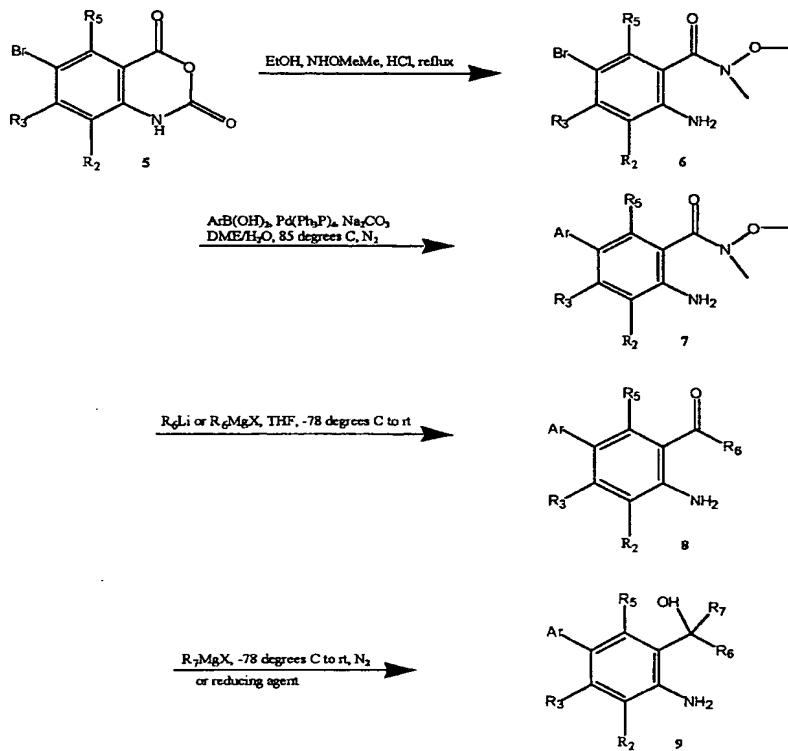
with phosphino ligands, e.g., Ph₃P, dppf, dppe or a catalyst such as palladium acetate. Under this catalytic condition, an appropriately substituted nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, is coupled with amino carbinol 2 to give 3. If a base is needed in the reaction, the commonly used bases include but not limited to sodium bicarbonate, sodium carbonate, potassium phosphate, barium carbonate, cesium fluoride, or potassium acetate. The most commonly used solvents in these reactions include benzene, DMF, isopropanol, ethanol, DME, ether, acetone, or a mixture of above solvent and water. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to 95 °C. The compounds of this invention 4 can be effected by treatment of amino carbinol 3 with an appropriate ketone in the presence of an suitable acid catalyst such as *p*-toluenesulfonic acid in a suitable solvent such as toluene, benzene under an inert atmosphere such as argon or nitrogen at room temperature to reflux.

Scheme II describes the procedure to prepare benzoxazines bearing two different substituents at position-4. The Weinreb amide 6 can be prepared from an appropriately substituted isatoic anhydride 5 when treated with *N*-, *O*-dimethylhydroxyl-amine hydrochloride salt in a protic solvent such as ethanol, or isopropanol at reflux under an inert atmosphere such as argon or nitrogen. Coupling of amide 6 with an aryl electrophile such as aryl boronic acid or arylstannane to give 7 can be effected by employing a typical coupling reaction such as Suzuki, Stille coupling procedure in a similar fashion as described for the preparation of compound 3. Treatment of Weinreb amide 7 with organo metallic compounds, e.g., alkylolithium, alkynyllithium, aryllithium, or their Grignard counterpart in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78 °C to room temperature affords amino ketone 8. Conversion of ketone 8 to carbinol 9 can be effected by treatment of 8 with an organo metallic reagent such as alkyl, alkynyl, or aryl Grignard reagent in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78 °C to room temperature. Conversion of

- 25 -

ketone **8** to carbinol **9** can also be effected by reduction of ketone group of **8** to the carbinol moiety of **9** using an appropriate reducing reagent such as lithium aluminum hydride, sodium borohydride in a suitable solvent such as THF, ether, or anhydrous alcohol under an inert atmosphere in the temperature ranging from 0 °C to the boiling point of the solvent. Further conversion of **9** to the compounds of this invention can be effected as described in scheme I for the preparation of compound **4**.

Scheme II

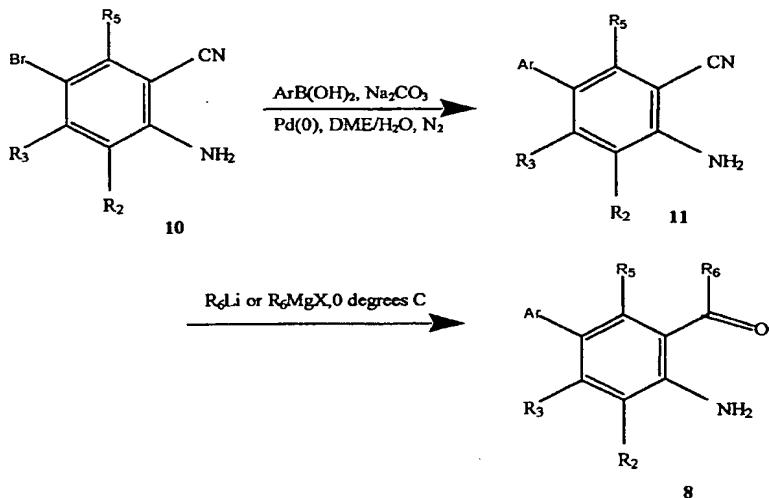


Alternatively, ortho-amino ketone **8** can be prepared by treatment of ortho-
10 amino benzonitrile **11** with an organo metallic compound such as organo lithium
reagent or Grignard reagent in a suitable solvent such as THF or ether under an inert

- 26 -

atmosphere such as argon or nitrogen at temperatures ranging from -78 °C to room temperature as illustrated in Scheme III. Benzonitrile **11** can be readily prepared from an appropriately substituted benzonitrile such as bromobenzonitrile **10** using a suitable coupling reaction such as Stille or Suzuki protocol carried out in a similar fashion as described for the preparation of the Weinreb amide **7**.

Scheme III



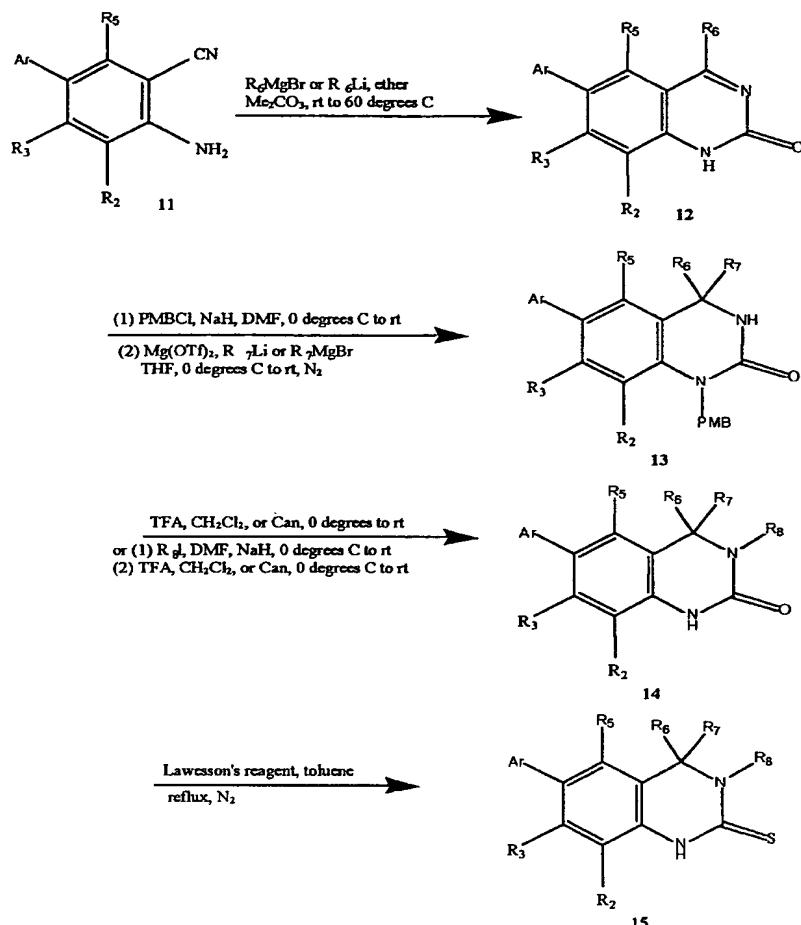
Scheme IV illustrates the synthesis of 3,4-dihydroquinazolin-2-ones. The substituted 2-aminobenzonitrile **11** is treated with an organo metallic reagent such as organo lithium or Grignard reagent in a nonprotic solvent such as THF or ether under an inert atmosphere such argon or nitrogen at -78 °C to room temperature to produce an imino intermediate which is reacted with a suitable carbonate such as diethyl carbonate or dimethyl carbonate *in situ* at 0 °C to 60 °C to give quinazolin-2-ones **12**. Protection of quinazolin-2-ones **12** with a suitable protective group such as para-methoxybenzyl moiety can be effected by treating **12** with a suitable base such as potassium hydride, potassium *t*-butoxide, or sodium hydride followed by addition of a protective reagent such as para-methoxybenzyl chloride in an appropriate solvent such

- 27 -

as DMF, or a mixture of solvents such as THF and DMF under an inert atmosphere such as nitrogen or argon at 0 °C to room temperature. The Michael addition of a suitable organo metallic compound such as organo lithium or Grignard reagent to the protected quinazolin-2-ones 12 to give 13 can be accomplished in the presence of a 5 suitable Lewis acid such as magnesium triflate in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at 0 °C to room temperature.

- 28 -

Scheme IV



Removal of protective group can be effected by treating **13** with a suitable deprotecting reagent, e.g. for the *para*-methoxybenzyl protective group it can be removed by treatment of **13** with protic acid such as TFA or with Ceric ammonium nitrate in a suitable solvent such as methylene chloride at 0°C to room temperature under an inert atmosphere such as argon or nitrogen. Prior to the removal of protective group, the alkylation of 3-nitrogen can be achieved by treating **13** with an

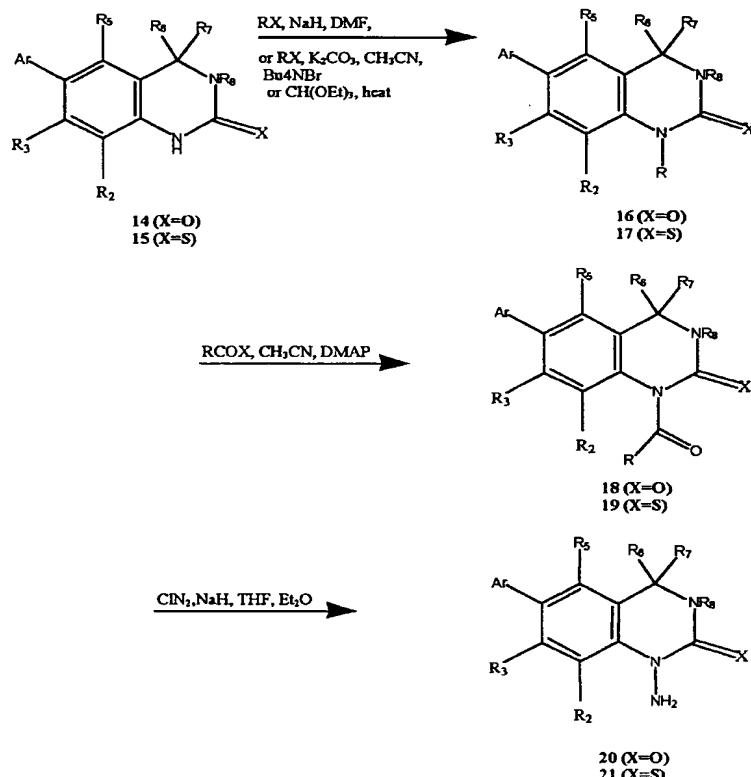
appropriate base such as sodium hydride, potassium hydride, or potassium *t*-butoxide in a suitable solvent such as DMF followed by quenching the reaction solution with an organo iodide or an organo triflate such as iodomethane under an inert atmosphere such as argon or nitrogen at 0°C to room temperature. The compounds of the present
5 invention **14** can be accomplished when the protective group is removed with a suitable reagent, e.g. for the *para*-methoxybenzyl protective group it can be removed by treatment of **13** with protic acid such as TFA or with Ceric ammonium nitrate in a suitable solvent such as methylene chloride at 0°C to room temperature under an inert atmosphere such as argon or nitrogen.

10 The conversion of compounds **14** to 3,4-dihydroquinazolin-2-thiones **15** can be accomplished by treatment of **14** with a suitable sulfur reagent such as Lawesson's reagent in a nonprotic solvent such as o-xylene, chlorobenzene, or toluene under an inert atmosphere such as argon or nitrogen at reflux.

15 As illustrated in scheme V, the compounds **14** or **15** can be further derivatized at position-1 *via* numerous approaches leading to a variety of the novel derivatives including 1-alkyl, substituted 1-alkyl, 1-carbonyl, substituted 1-carbonyl, 1-carboxy, substituted 1-carboxy derivatives. For examples, alkyl or substituted alkyl derivatives
20 **16** or **17** can be effected by treatment of carbamate **14** or **15** with a suitable base such as sodium hydride in a suitable solvent such as DMF under an inert atmosphere such as argon or nitrogen followed by addition of an appropriate electrophile such as alkyl or substituted alkyl bromide, iodide, or triflate. Such transformation of **14** or **15** to **16** or
25 **17** at position-1 can also be effected using biphasic condition as indicated in scheme V in which alkylation is executed using a biphasic catalyst such as tributylammonium bromide in a suitable solvent such as acetonitrile. A further example of such modification in position-1 includes but not limited to the one depicted in scheme V in that heating of **14** or **15** with triethyl orthoformate affords 1-substituted derivatives of compound **14** or **15**.

- 30 -

Scheme V



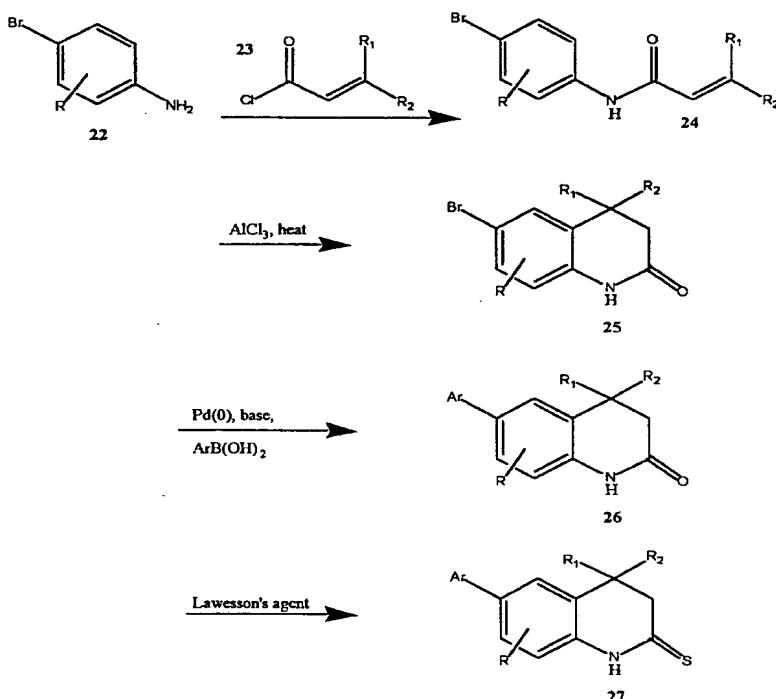
The acylation or carboxylation of the compound 14 or 15 at position-1 to give compound 18 or 19 can be readily effected by treatment of 14 or 15 with a suitable acylating or carboxylating reagent such as di-*t*-butyl dicarbonate in the presence of a suitable basic catalyst such as DMAP in a suitable solvent such as acetonitrile under an inert atmosphere such as argon or nitrogen. The amination of position-1 of compound 14 or 15 to give compounds 20 and 21 can be furnished using a suitable aminating reagent such as chloroamine in the presence of a suitable base such as sodium hydride

- 31 -

in a suitable solvent such as THF or diethyl ether following the literature procedure (Metlesics et al. *J. Org. Chem.* 30, 1311(1965).).

According to scheme VI an appropriate aniline such as 4-bromoaniline **22**, is reacted in the presence of a base in a suitable nonprotic solvent with an acryloyl chloride **23** to form the amide **24**. The base is preferably a strong base such as sodium hydride or sodium or potassium hexamethyldisilylamide, utilizing THF as the solvent under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.

Scheme VI



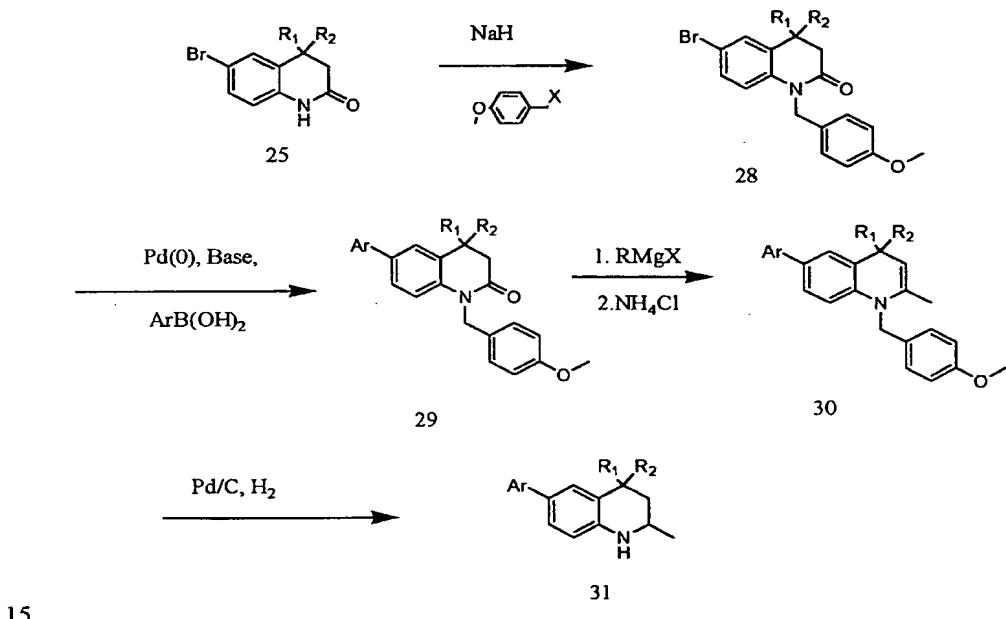
10

Reaction of the amide **24** under strongly acidic conditions, sulfuric acid, boron trifluoride etherate, or preferably aluminum chloride either as a melt, or in an

inert solvent (dichlorobenzenes) under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature, of the solvent then provides the cyclic amide 25. Subsequent reaction of compound 25 with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound 5 26. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or THF, under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.

10 The conversion of compounds 26 to thioamide 27 can be accomplished by treatment of 26 with a suitable sulfur reagent such as Lawesson's reagent in a nonprotic solvent such as o-xylene, chlorobenzene, or toluene under an inert atmosphere such as argon or nitrogen at reflux.

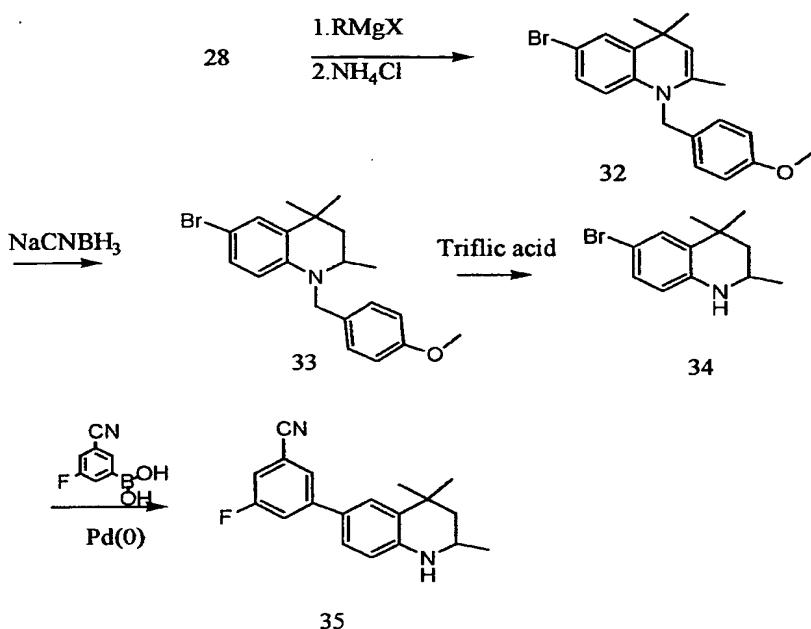
Scheme VII



According to scheme VII, an appropriate cyclic amide such as **25**, is allowed to react with NaH in THF to form the anion species and then a benzyl halide is added to convert the starting material to the N-protected amide product, **28**. Reaction of **28** with an aryl boronic acid in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium acetate permits a coupling of the two aromatic species to yield **29**. The reaction is normally carried out under biphasic conditions. That is, water is often employed along with an appropriate organic solvent, such as toluene or DMF. The palladium catalyst is typically added last and the reaction mixture is refluxed in the presence of an inert gas such as nitrogen. The product is treated with a Grignard Reagent, an alkyl magnesium halide, in THF followed by the addition of ammonium chloride solution to afford the enamine derivative **30**. The reduction of the double bond in **30** and removal of the protecting group can be accomplished in a single step by catalytic reduction in a Parr Hydrogenation Apparatus using palladium on charcoal to form the target compound **31**.

- 34 -

Scheme VIII



3-Fluoro-5-(2,4,4-trimethyl-1,2,3,4-hydro-quinolinyl)-benzonitrile (compound 35) can be prepared by Scheme VIII, a process similar to Scheme VII. According to scheme VIII, compound 28 is allowed to react with a Grignard reagent, an alkyl 5 magnesium halide, in THF followed by the addition of ammonium chloride solution to afford the enamine derivative 32. Reduction of the double bond with sodium cyanoborohydride affords the reduced derivative 33. Removal of the protecting group with a strong acid such as triflic or sulfuric acid affords the deprotected compound 34 which can then be coupled with a suitably substituted phenylboronic acid in the 10 presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium acetate permits a coupling of the two aromatic species to yield 35. The

reaction is normally carried out under biphasic conditions. That is, water is often employed along with an appropriate organic solvent, such as toluene or DMF.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These 5 salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other 10 conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

This invention includes pharmaceutical compositions and treatments which comprise administering to a mammal a pharmaceutically effective amount of one or more compounds as described above wherein G₂ is C=O as antagonists of the 15 progesterone receptor. The invention further provides comparable methods and compositions which utilize one or more compounds herein wherein G₂ is C=S as agonists of the progesterone receptor. Moreover the invention further provides comparable methods and compositions which utilize one or more compounds herein wherein G₁=O and G₂=CR₇CR₈ are agonists of the progesterone receptor and when 20 G₁=CR₇CR₈ and G₂=CR₇CR₈ are antagonists of the progesterone receptor.

The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the 25 compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock. When used in contraception the progesterone receptor antagonists of the

current invention may be used either alone in a continuous administration of between 1 and 500 mg per day, or alternatively used in a different regimen which would entail 2-4 days of treatment with the progesterone receptor antagonist after 21 days of a progestin, in this regimen between 0.1 and 500 mg daily doses of the progestin (e.g. 5 levonorgestrel, trimegestone, gestodene, norethisterone acetate, norgestimate or cyproterone acetate) would be followed by between 0.1 and 500 mg daily doses of the progesterone receptor antagonists of the current invention.

The progesterone receptor antagonists of this invention, used alone or in combination, can also be utilized in methods of treatment and/or prevention of benign 10 and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present 15 progesterone receptor antagonists include the synchronization of the estrus in livestock.

The progesterone receptor agonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic 20 ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake.

When used in contraception the progesterone receptor agonists of the current invention are preferably used in combination or sequentially with an estrogen agonist (e.g. ethinyl estradiol). The preferred dose of the progesterone receptor agonist is 25 between 0.01 and 500 mg per day.

When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for

example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and

must be fluid to the extent that easy syringe ability exists. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g.,
5 glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The following non-limiting examples are illustrative of the invention.

EXAMPLE 1

10 **1-(4-Amino-3'-chloro-biphenyl-3-yl)-ethanone**

A mixture of 2-amino-5-bromo-N-methoxy-N-methylbenzamide (7.78g, 30 mmol), 3-chlorophenyl boronic acid (5.63g, 36 mmol), tetrakis(triphenylphosphine)palladium (0) (1.73g, 1.5 mmol), and sodium carbonate (7.63g, 72 mmol) in a mixture of DME and water (150 mL/30 mL) was degassed to
15 remove the oxygen and was then heated at 85 °C under nitrogen for 3 hours. The reaction mixture was cooled to room temperature and treated with brine (30 mL) and ethyl acetate (100 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine and dried with MgSO₄. After removal of solvent, the residue was purified
20 by a flash chromatography (silica gel, hexane:ethyl acetate/1:1) to give 5-(3-chlorophenyl)-N-methoxy-N-methylbenzamide as a brown oil (5g, 57%). To a solution of this benzamide (5g, 17.2 mmol) in anhydrous THF was added in a dropwise fashion a solution of methylolithium in ether (1.4M, 28.6 mL, 40 mL) at -78 °C under nitrogen. After stirring for 30 minutes, the reaction mixture was treated with
25 a saturated aqueous ammonium chloride solution (50 mL) at -78 °C. Ethyl acetate (100 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed (brine) and dried (MgSO₄). After removal of solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/2:1) to afford 1-(4-amino-3'-

- 39 -

chloro-biphenyl-3-yl)-ethanone as yellow solid (2g, 47%): mp 89-90 °C; ¹H-NMR (CDCl₃) δ 7.89 (d, 1H, J = 2.0 Hz), 7.51 (m, 2H), 7.25-7.40 (m, 3H), 6.73 (d, 1H, J = 8.6 Hz), 6.38 (br, 2H), 2.65 (s, 3H); MS (EI) m/z 268([M+Na]⁺, 60%); Anal. Calc. For C₁₄H₁₂CINO: C, 68.44, H, 4.92, N, 5.70. Found: C, 68.40, H, 4.89, N, 5.61.

5

EXAMPLE 2

1-(4-Amino-3'-chloro-biphenyl-3-yl)-dimethyl-methanol

To a solution of 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone (.55g, 2.2 mmol) in anhydrous THF under nitrogen was added a solution of methyl magnesium bromide (3.0 M in diethyl ether, 1 mL, 3 mmol) at 0 °C. The mixture was slowly warmed to room temperature and kept stirring under nitrogen for 18 hours. The mixture was treated with 10 mL of saturated ammonium chloride aqueous solution and ethyl acetate (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with brine (20 mL) and dried (MgSO₄). After removal of the solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/2:1) to afford the title compound as an off-white solid: 186-188 °C (HCl salt). Anal. Calc. For C₁₅H₁₇Cl₂NO: C, 60.42, H, 5.75, N, 4.7. Found: C, 60.51, H, 5.62, N, 4.56.

20

EXAMPLE 3

6-(3-Chloro-phenyl)-2,4,4-trimethyl-2-trifluoromethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine

A mixture of (4-amino-3'-chloro-biphenyl-3-yl)-dimethyl-methanol (0.25 g, 0.95 mmol), trifluoromethylacetone (0.16 g, 1.43 mmol), and p-toluenesulfonic acid (0.01 g, 0.05 mmol) in dry toluene (5 mL) was stirred under a blanket of nitrogen for 48 hours. Upon completion of the reaction, the toluene was removed and the residue purified via flash chromatography (silica gel, 10% ethyl acetate/hexane) to give 6-(3-chloro-phenyl)-2,4,4-trimethyl-2-trifluoromethyl-1,4-dihydro-2H-benzo[d][1,3]-oxazine (0.22 g, 65%) as a clear oil. The oil was dissolved in ether at -78 °C and then

- 40 -

treated with a solution of 1N HCl in ether to give the hydrochloride salt of the title compound as a white solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 7.67 (bs, 1H), 7.58 (d, 1H, J = 7.88 Hz), 7.42 (m, 3H), 7.32 (d, 1H, J = 7.96 Hz), 6.84 (d, 1H, J = 8.03 Hz), 1.52 (s, 3H), 1.5 (s, 6H); MS (APCI) m/z 354 ([M-H] $^+$, 100%); Anal. Calc. For 5 $\text{C}_{18}\text{H}_{17}\text{ClF}_3\text{NO}$: C, 55.12; H, 4.62; N, 3.57. Found: C, 54.97; H, 4.59; N, 3.41.

EXAMPLE 4

6-(3-Chloro-phenyl)-2,2,4,4-tetramethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine

A mixture of (4-amino-3'-chloro-biphenyl-3-yl)-dimethyl-methanol (0.46 g, 1.8 10 mmol), acetone (0.16 g, 2.7 mmol), and *p*-toluenesulfonic acid (0.017 g, 0.09 mmol) in dry toluene (6 mL) was heated at 33 °C under a blanket of nitrogen overnight. Upon completion of the reaction, the toluene was removed and the compound purified via a flash chromatography (silica gel, 15% ethyl acetate/hexane) to give 6-(3-chloro-phenyl)-2,2,4,4-tetramethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (0.36 g, 68%) as a 15 yellow oil. The oil was dissolved in ether at -78 °C and then treated with a solution of 1N HCl in ether to give the hydrochloride salt of the title compound as a yellow solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 7.70 (bs, 1H), 7.61 (d, 1H, J = 7.82 Hz), 7.52 (bs, 1H), 7.44 (m, 2H), 7.33 (d, 1H, J = 8.21 Hz), 6.87 (d, 1H, J = 7.85 Hz), 1.5 (s, 6H), 1.4 (s, 6H); MS (ESI) m/z 302 ([M+H] $^+$, 100%); Anal. Calc. For $\text{C}_{18}\text{H}_{20}\text{ClNO}$: C, 63.91; H, 20 6.26; N, 4.14. Found: C, 64.08; H, 6.43; N, 4.14.

EXAMPLE 5

6-(3-Nitro-phenyl)-2,2,4,-trimethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine

Prepared from 1-(4-amino-3'-nitro-biphenyl-3-yl)-ethanol and acetone in the 25 same fashion as that of Example 4. Yellow solid: mp 188-189 °C; Anal. Calc. For $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3 \cdot 0.35 \text{ H}_2\text{O}$: C, 67.02; H, 6.19; N, 9.20. Found: C, 66.7; H, 5.89; N, 9.03.

- 41 -

EXAMPLE 6

4-Amino-3'-chloro-biphenyl-3-carbonitrile

A mixture of 2-amino-5-bromobenzonitrile (10g, 50 mmol), 3-chlorophenyl boronic acid (9.5g, 60 mmol), tetrakis(triphenylphosphine)-palladium (0) (3.5g, 3 mmol), and sodium carbonate (13g, 120 mmol) in a mixture of DME and water (100 mL/25 mL) was degassed to remove the oxygen and then heated to 85 °C under a blanket of nitrogen for 5 hours. The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous ammonium chloride solution (80 mL). Ethyl acetate (200 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine and dried with MgSO₄. The solvent was removed *in vacuo* and the residue was purified by a silica gel flash chromatography (hexane:ethyl acetate/4:1) to afford 4-amino-3'-chloro-biphenyl-3-carbonitrile as an off-white solid (8g, 87%): mp 118-119 °C; ¹H-NMR (DMSO-d₆) δ 7.80 (d, 1H, J = 2.3 Hz), 7.65-10 7.72 (m, 2H), 7.57 (d, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 7.9 Hz), 7.31 (m, 1H), 6.87 (d, 1H, J = 8.7 Hz), 6.29 (br, 2H); Anal. Calc. For C₁₃H₉CIN₂: C, 68.28, H, 3.97, N, 12.25. Found: C, 67.68, H, 4.06, N, 11.89.

EXAMPLE 7

6-(3-Chlorophenyl)-4-cyclopropyl-1H-quinazolin-2-one

Prepared using a similar procedure as described in the literature (Tucker et al. *J. Med. Chem.*, 1994, 37, 2437-2444). To a solution of cyclopropylmagnesium bromide prepared from magnesium (0.9g, 37 mmol) and cyclopropyl bromide (3.2 mL, 40 mmol) in anhydrous THF was added at 50 °C under nitrogen a solution of 4-amino-25 3'-chloro-biphenyl-3-carbonitrile (2.3g, 10 mmol) in anhydrous THF. After addition, the reaction mixture was kept at 50 °C for 30 minutes under nitrogen and treated with dimethyl carbonate in a dropwise manner. The reaction solution was stirred at 50 °C under nitrogen for 30 minutes and cooled to ambient temperature. A saturated aqueous ammonium chloride solution (30 mL) was added followed by addition of ethyl

- 42 -

acetate (80 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine and dried with MgSO₄. After removal of the solvent, the residue was purified by a flash chromatography (silica gel, methylene chloride:methanol/25:1) to give 6-(3-chlorophenyl)-4-cyclopropyl-1H-quinazolin-2-one as a yellowish solid (0.55g, 18%): mp 189-190 °C; ¹H-NMR (DMSO-d₆) δ 11.71 (s, 1H, D₂O exchangeable), 8.56 (d, 1H, J = 1.3 Hz), 8.09 (dd, 1H, J = 8.6, 1.6 Hz), 7.92 (s, 1H), 7.77 (d, 1H, J = 7.7 Hz), 7.52 (t, 1H, J = 7.9 Hz), 7.45 (d, 1H, J = 8.1 Hz), 7.36 (d, 1H, J = 8.6 Hz), 3.15 (m, 1H), 1.20 (m, 4H); MS (Cl) m/z 297 ([M+H]⁺, 100%); Anal. Calc. For C₁₇H₁₃ClN₂O: C, 69.98, H, 4.49, N, 9.23. Found: C, 67.98, H, 4.46, N, 9.10.

EXAMPLE 8

6-(3-Chlorophenyl)-4-cyclopropyl-1-(4-methoxybenzyl)-1H-quinazolin-2-one

To a suspension of 6-(3-chlorophenyl)-4-cyclopropyl-1H-quinazolin-2-one (0.5g, 1.68 mmol) in anhydrous DMF was added potassium hexamethylsilyl amide (0.45g, 2.1 mmol) at ambient temperature under nitrogen. The reaction mixture was stirred at ambient temperature for 30 minutes, treated with *p*-methoxy benzyl chloride (0.35 mL, 2.5 mmol), and heated at 55°C for 5 hours. The mixture was then cooled to room temperature and quenched with a saturated aqueous ammonium chloride solution (10 mL). Methylene chloride (50 mL) was added and organic layer was separated. The aqueous layer was extracted with methylene chloride (2x20 mL) and the combined organic layers were washed with brine and dried (MgSO₄). After removal of solvent, the residue was separated on a flash chromatography (silica gel, hexane:ethyl acetate/1:1) to afford 6-(3-chlorophenyl)-4-cyclopropyl-1-(4-methoxybenzyl)-1H-quinazolin-2-one as an off-white solid: mp 173-174 °C; ¹H-NMR (DMSO-d₆) δ 8.65 (d, 1H, J = 1.8 Hz), 8.10 (dd, 1H, J = 8.9, 1.8 Hz), 7.93 (d, 1H, J = 1.6 Hz), 7.79 (d, 1H, J = 7.6 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.46 (t, 1H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 5.41 (s, 2H), 3.73 (s, 3H), 3.18 (m, 1H), 1.18-1.27

(m, 4H); MS (CI) m/z 417([M+H]⁺, 100%); Anal. Calc. For C₂₅H₂₁ClN₂O₂: C, 72.02, H, 5.08, N, 6.72. Found: C, 71.88, H, 4.91, N, 6.70.

6-(3-Chlorophenyl)-4-cyclopropyl-2-(4-methoxybenzyloxy)quinazoline was obtained as a side product, off-white solid: mp 158-159 °C; ¹H-NMR (DMSO-d₆) δ 5 8.75 (d, 1H, J = 1.7 Hz), 8.26 (dd, 1H, J = 8.8, 1.8 Hz), 8.01 (s, 1H), 7.84 (m, 2H), 7.56 (t, 1H, J = 7.9 Hz), 7.45 (m, 3H), 6.96 (d, 2H, J = 8.6 Hz), 5.38 (s, 2H), 3.75 (s, 3H), 3.24 (m, 1H), 1.25 (m, 4H); MS (CI) m/z 417([M+H]⁺, 100%); Anal. Calc. For C₂₅H₂₁ClN₂O₂: C, 72.02, H, 5.08, N, 6.72. Found: C, 72.19, H, 4.91, N, 6.65.

10

EXAMPLE 9**6-(3-Chlorophenyl)-4-cyclopropyl-4-methyl-3,4-dihydro-1H-quinazolin-2-one**

To a solution of 6-(3-chlorophenyl)-4-cyclopropyl-1-(4-methoxybenzyl)-1H-quinazolin-2-one (0.25g, 0.6 mmol) in anhydrous ether was added, at ambient 15 temperature under nitrogen, magnesium triflate (0.78g, 2.4 mmol). The mixture was stirred for 30 minutes and treated with a solution of methylmagnesium bromide in ether (3.0 M, 1.0 mL, 3.0 mmol). The reaction mixture was kept at room temperature under nitrogen for 3 hours and quenched with a mixture of a saturated aqueous ammonium chloride solution (10 mL) and 1N aqueous HCl solution (5 mL). The 20 mixture was stirred at room temperature for 20 minutes and ethyl acetate (40 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine and dried (MgSO₄). The solvent was removed and a half portion of the residue was dissolved in TFA (3 mL) and was stirred under nitrogen at room temperature for 72 25 hours. The solution was poured onto ice-water and the white precipitate obtained was collected on a filter. The solid was washed with water and then purified by a flash chromatography (methylene chloride:methanol/25:1, silica gel) to give 6-(3-chlorophenyl)-4-cyclopropyl-4-methyl-3,4-dihydro-1H-quinazolin-2-one as off-white solid(40 mg, 43%): mp 125-127 °C; ¹H-NMR (DMSO-d₆) δ 9.21 (s, 1H), 7.71 (s,

- 44 -

1H), 7.61 (d, 1H, $J = 7.8$ Hz), 7.55 (d, 1H, $J = 1.6$ Hz), 7.47 (dd, 1H, $J = 8.3, 1.8$ Hz), 7.45 (t, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 8.1$ Hz), 6.84 (d, 1H, $J = 8.2$ Hz), 6.79 (s, 1H), 1.54 (s, 3H), 1.11 (m, 1H), 0.42 (m, 1H), 0.15-0.20 (m, 3H); MS (ESI) m/z 313([M+H]⁺, 100%).

5

EXAMPLE 10

6-(3-Chlorophenyl)-4-cyclopropyl-3,4-dimethyl-3,4-dihydro-1H-quinazolin-2-one

To a solution of half of the crude addition product from Example 9 in anhydrous DMF (5 mL) was added under nitrogen at room temperature sodium hydride (25 mg, 0.63 mmol). The mixture was stirred at ambient temperature for 30 minutes and treated with methyl iodide (0.5 mL, excess). After stirring for 3.5 hours, a mixture of saturated aqueous ammonium chloride and 1N HCl aqueous solution (10 mL/5 mL) was added to the reaction mixture. Ethyl acetate (30 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x10 mL) and the combined organic layers were washed with brine and dried (MgSO_4). The solvent was removed and residue was dissolved in a mixture of methylene chloride and TFA (2 mL/2 mL). After stirring for 3 hours, the solution was poured onto ice-water and neutralized by addition of a saturated aqueous sodium bicarbonate solution. The ethyl acetate (30 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine and dried (MgSO_4). The solvent was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/1:1) to afford 6-(3-chlorophenyl)-4-cyclopropyl-3,4-dimethyl-3,4-dihydro-1H-quinazolin-2-one as a white solid (11 mg, 11% for three steps): mp 193-194 °C; ¹H-NMR (DMSO- d_6) δ 9.51 (s, 1H), 7.68 (s, 1H), 7.59 (d, 1H, $J = 8.0$ Hz), 7.57 (d, 1H, $J = 1.6$ Hz), 7.51 (dd, 1H, $J = 8.3, 1.7$ Hz), 7.46 (t, 1H, $J = 7.8$ Hz), 7.35 (d, 1H, $J = 8.1$ Hz), 6.87 (d, 1H, $J = 8.3$ Hz), 3.02 (s, 3H), 1.51 (s, 3H), 1.25 (m, 1H), 0.32-0.51 (m, 3H), 0.25 (m, 1H); MS (CI) m/z 327 ([M+H]⁺, 100%). Anal. Calc. For $C_{19}H_{19}ClN_2O \cdot 0.3 H_2O$: C, 68.69, H, 5.95, N, 8.43. Found: C, 68.69, H, 5.70, N, 8.18.

- 45 -

EXAMPLE 11

6-(3-Chloro-phenyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one

- Sodium hydride (1.16 g, ca 29 mmol, 60% in oil) was washed with hexane (x3) 5 then placed in anhydrous THF (50 mL) under nitrogen. To this slurry was then added dropwise a solution of 4-bromoaniline (5.0 g, 29 mmol) in dry THF (100 mL). After 0.5 h, the mixture was cooled to 0 °C and treated with a solution of 3,3-dimethylacryloyl chloride in anhydrous THF (30 mL). After 4 h, the mixture was quenched with saturated aqueous ammonium chloride solution, and extracted with diethyl ether. The organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was then crystallized from EtOAc/hexane to afford *N*-(3,3'-dimethylacryloyl)-4-bromoaniline (3.36 g, 13.22 mmol, 46%) as a white solid: ^1H NMR (CDCl_3) δ 7.42 (s, 4H), 7.06 (s, 1H), 5.68 (s, 1H), 2.21 (s, 3H), 1.09 (s, 3H); MS (EI) m/z 253 [M^+].
- 15 *N*-(3,3'-Dimethylacryloyl)-4-bromoaniline (4.0 g, 15.38 mmol) was heated under nitrogen to ca. 130 - 140 °C causing the solid to melt. Aluminum chloride (3.07 g, 23 mmol) was added and heating continued. After 1 h, the mixture was cooled and quenched carefully with water and then extracted with dichloromethane (3x60 mL). The combined organic layers were washed with water, dried (MgSO_4) and evaporated.
- 20 The residue was then subjected to column chromatography (SiO_2 , EtOAc/hexane gradient elution) to afford 6-bromo-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (1.69 g, 6.6 mmol, 47%) as a white solid: $^1\text{H-NMR}$ (CDCl_3) δ 8.82 (s, 1H), 7.39 (d, 1H, J = 2 Hz), 7.29 (dd, 1H, J = 8.3, 2.0 Hz), 6.71 (d, 1H, J = 8.0 Hz), 2.47 (s, 2H), 1.32 (s, 6H).
- 25 To a solution of the last cited compound (0.5 g, 1.96 mmol) in dimethoxyethane (15 mL) was added tetrakis(triphenylphosphine)palladium (0) (0.11 g, 0.09 mmol) under nitrogen. After 15 min., 3-chlorophenylboronic acid (0.6 g, 3.9 mmol) was added followed by potassium carbonate (1.62 g, 11.7 mmol) in water (7.5 mL). After 1.5 h at reflux, the mixture was cooled, filtered, and extracted with

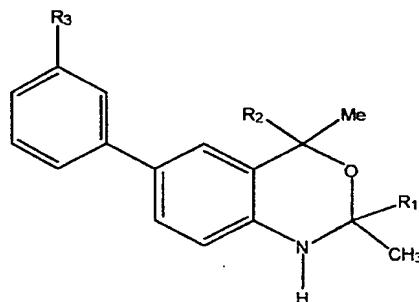
- 46 -

EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was then subjected to column chromatography (SiO_2 , EtOAc:hexane/3:1) and crystallized from dichloromethane/hexane to afford 6-(3-chloro-phenyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (0.21 g, 0.73 mmol, 37%) as a white solid; 5 mp. 211 - 215 °C; 1H -NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.53 (s, 1H), 7.47 (d, 1H, J = 2.0 Hz), 7.44 - 7.29 (m, 4H), 6.87 (1H, d, J = 2.0 Hz), 2.54 (s, 2H), 1.39 (s, 6H); MS ((-ES) m/z 284 [M-H]⁺.

EXAMPLE 12 – Pharmacology

10 The compounds of this invention were tested in the relevant assay as described below and their potency are in the range of 0.01 nM to 5 μ M in the *in vitro* assays and 0.001 to 300 mg/kg in the *in vivo* assays. The selected examples are listed below

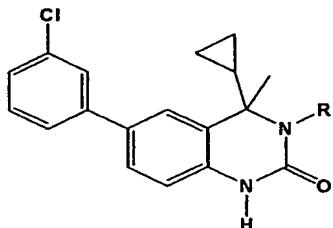
Table 1



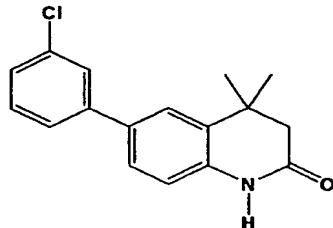
15

Compound	R_1	R_2	R_3	hPR CV-1	
				IC_{50} (nM)	
1	Me	Me	Cl	10.0	
2	CF_3	Me	Cl	50.0	
3	Me	H	NO_2	1675	

- 47 -



R = H, hPR CV-1, IC₅₀ = 1075 nM



hPR CV-1, IC₅₀ = 1075 nM

R = Me, hPR CV-1, IC₅₀ = 580 nM

5

A. In-vitro biology

The in-vitro biology is determined by (1) competitive Radioligand Binding: using the A-form of the human progesterone receptor with progesterone as the radioligand; (2) co-transfection assay, which provides functional activity expressed as agonist EC₅₀ and Antagonist IC₅₀ values; (3) a T47D cell proliferation, which is a further functional assay which also provides agonist and antagonist data; and (4) T47D cell alkaline phosphatase assay, which is a further functional assay which also provides agonist and antagonist data.

10 1. hPR Binding assay - This assay is carried out in accordance with: Pathirana, C.; Stein, R.B.; Berger, T.S.; Fenical, W.; Ianiro, T.; Mais, D.E.; Torres, A.; Glodman, M.E., *Nonsteroidal human progesterone receptor modulators from the marine alga cymoplia barbata*, J. Steroid Biochem. Mol. Biol., 1992, 41, 733-738.

15 2. PRE-luciferase assay in CV-1 cells

20 The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1

mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows:
5 DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium.
Co-transfection is done using 1.2×10^7 cells, 5 mg pLEM plasmid with hPR-B inserted
10 at SphI and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II.
After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 μ l. Following overnight incubation, the medium is
15 changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty μ l of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are
20 shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

- 49 -

d. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC₅₀ or IC₅₀ values are calculated.

5

Table 2. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

	<u>Compound</u>	<u>Exp.</u>	<u>EC₅₀</u>		<u>95% CI</u>	
			(nM)	SE	lower	upper
10	Progesterone	1	0.616	0.026	0.509	0.746
		2	0.402	0.019	0.323	0.501
		3	0.486	0.028	0.371	0.637
15	Trimegestone	1	0.0075	0.0002	0.0066	0.0085
		2	0.0081	0.0003	0.0070	0.0094
		3	0.0067	0.0003	0.0055	0.0082

20 **Table 3. Estimated IC₅₀, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies**

	<u>Compound</u>	<u>Exp.</u>	<u>IC₅₀</u>		<u>95% CI</u>	
			(nM)	SE	lower	upper
25	RU486	1	0.028	0.002	0.019	0.042
		2	0.037	0.002	0.029	0.048
		3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly (p<0.05) compared to vehicle control are considered active.

30 Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly (p<0.05)

- 50 -

EC₅₀: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC₅₀: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

5 3. T47D cell proliferation assay

The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The materials and methods used in this assay are as follows.

10 a. Growth medium: DMEM:F12 (1:1)

(GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

15 b. Treatment medium: Minimum Essential

Medium (MEM) (#51200-038GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment.

Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progestin and antiprogestin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progestin agonist. Twenty-four hours after treatment, the medium is

- 51 -

discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 μ l of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

e. Analysis of Results:

Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC₅₀ or IC₅₀ values are calculated.

- 52 -

Table 4. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for individual studies

	<u>Compound</u>	<u>Exp</u>	<u>EC₅₀</u>	<u>95% CI</u>	
			(nM)	SE	lower upper
5	Trimegestone	1	0.017	0.003	0.007 0.040
		2	0.014	0.001	0.011 0.017
		3	0.019	0.001	0.016 0.024
10	MPA	1	0.019	0.001	0.013 0.027
		2	0.017	0.001	0.011 0.024

Table 5. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU486

	<u>Compound</u>	<u>Exp</u>	<u>IC₅₀</u>	<u>95% CI</u>	
			(nM)	SE	lower upper
15	RU486	1	0.011	0.001	0.008 0.014
		2	0.016	0.001	0.014 0.020
		3	0.018	0.001	0.014 0.022

EC₅₀: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC₅₀: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

25 4. T47D cell alkaline phosphatase assay

The purpose of this assay is to identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells. The materials and methods used in this assay are as follows.

a. Culture medium: DMEM:F12 (1:1) (GIBCO, BRL)

30 supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 µg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

- 53 -

b. Alkaline phosphatase assay buffer:

- I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100
- II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

5

c. Cell Culture and Treatment:

Frozen T47D cells were thawed in a 37°C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 µl of diluted cell suspension was added. Twenty µl of reference or test compounds diluted in the culture medium was then added 10 to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO₂/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

At the end of treatment, the medium was removed 15 from the plate and fifty µl of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 µl of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

e. Analysis of Results: Analysis of dose-response data

20 For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the 25 retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

- 54 -

f. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the EC₅₀ or IC₅₀ values are calculated.

5

Table 6. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments

10	<u>Compound</u>	<u>Exp.</u>	<u>EC50</u>	<u>SE</u>	<u>95% CI</u>	
			(nM)		<u>lower</u>	<u>upper</u>
15	Progesterone	1	0.839	0.030	0.706	0.996
		2	0.639	0.006	0.611	0.669
		3	1.286	0.029	1.158	1.429
20	Trimegestone	1	0.084	0.002	0.076	0.091
		2	0.076	0.001	0.072	0.080
		3	0.160	0.004	0.141	0.181

25 Table 7. Estimated IC₅₀, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments

25	<u>Compound</u>	<u>Exp</u>	<u>IC 50</u>	<u>SE</u>	<u>95% CI</u>	
			(nM)		<u>lower</u>	<u>upper</u>
30	RU486	1	0.103	0.002	0.092	0.115
		2	0.120	0.001	0.115	0.126
		3	0.094	0.007	0.066	0.134

B. In-vivo Biology

The primary in-vivo assay is the rat decidualization model which may be used to determine progestational effects of both agonists and antagonists. The secondary in-

vivo assay is the rat ovulation inhibition model which is under development and hence the protocol is un-available.

1. Rat decidualization assay The objective of this procedure is used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and 5 compare the relative potencies of various test compounds. The materials and methods used in this assay are as follows.

a. Methods: Test compounds are dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (MazolaTM) are then prepared by heating (~80 °C) the mixture to evaporate ethanol. 10 Test compounds are subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

b. Animals (RACUC protocol #5002)

Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) 15 are obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy is performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals are housed under 12 hr light/dark cycle and given standard rat chow and water ad libitum.

c. Treatment

20 Rats are weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 ml vehicle are administered by subcutaneous injection in the nape of the neck or by lavage using 0.5 ml. The animals are treated once daily for seven days. For testing antiprogestins, animals are given the test compounds and a EC₅₀ dose of progesterone (5.6 mg/kg) during the first three days 25 of treatment. Following decidual stimulation, animals continue to receive progesterone until necropsy four days later.

d. Dosing

Doses are prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle is included. Determination of

- 56 -

dose-response curves is carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg...).

e. Decidual induction

Approximately 24 hr after the third injection, decidualization
5 is induced in one of the uterine horns by scratching the antimesometrial luminal
epithelium with a blunt 21 G needle. The contralateral horn is not scratched and serves
as an unstimulated control. Approximately 24 hr following the final treatment, rats are
sacrificed by CO₂ asphyxiation and body weight measured. Uteri are removed and
trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns are weighed
10 separately.

f. Analysis of Results:

The increase in weight of the decidualized uterine horn is
calculated by D-horn/C-horn and logarithmic transformation is used to maximize
normality and homogeneity of variance. The Huber M-estimator is used to down
15 weight the outlying transformed observations for both dose-response curve fitting and
one-way analysis of variance. JMP software (SAS Institute, Inc.) is used for both one-
way ANOVA and non-linear dose-response analyses.

g. Reference Compounds:

All progestin reference compounds were run in full dose-
20 response curves and the EC₅₀ for uterine wet weight were calculated.

- 57 -

Table 8. Estimated EC₅₀, standard error (SE), and 95% confidence intervals for individual studies

	Compound	Exp	EC ₅₀	95% CI	
			(mg/kg, s.c.)	SE	lower upper
5	Progesterone	1	5.50	0.77	4.21 7.20
		2	6.21	1.12	4.41 8.76
10	3-Ketodesogestrel	1	0.11	0.02	0.07 0.16
		2	0.10	0.05	0.11 0.25
		3	0.06	0.03	0.03 0.14
15	Levonorgestrel	1	0.08	0.03	0.04 0.16
		2	0.12	0.02	0.09 0.17
		3	0.09	0.02	0.06 0.13
		4	0.09	0.02	0.06 0.14
20	MPA	1	0.42	0.03	0.29 0.60
		2	0.39	0.05	0.22 0.67
		3	0.39	0.04	0.25 0.61

Table 9. Estimated average EC₅₀, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds

	Compound	EC ₅₀	95% CI	
		(mg/kg, s.c.)	SE	lower upper
	Progesterone	5.62	0.62	4.55 7.00
	3-Ketodesogestrel	0.10	0.02	0.07 0.14
30	Levonorgestrel	0.10	0.01	0.08 0.12

- 58 -

Table 10. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU 486

5

<u>Compound</u>	<u>Exp.</u>	<u>IC₅₀</u>	<u>95% CI</u>		
		(mg/kg, p.o.)	<u>SE</u>	<u>lower</u>	<u>upper</u>
RU 486	1	0.21	0.07	0.05	0.96
	2	0.14	0.02	0.08	0.27

10

Concentration: Compound concentration in assay(default-mg/kg body weight)

Route of administration: Route the compound is administered to the animals

Body weight: Mean total animal body weight (default-kg)

D-horn: Wet weight of decidualized uterine horn (default-mg)

15

C-horn: Wet weight of control uterine horn (default-mg)

Decidual response: [(D-C)/C]x100%

Progestational activity: Compounds that induce decidualization significantly (p<0.05) compared to vehicle control are considered active

20

Antiprogestational activity: Compounds that decrease EC₅₀ progesterone induced decidualization significantly (p<0.05)

EC₅₀ for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

IC₅₀ for uterine weight: Concentration of compound that gives half-maximal decrease in EC₅₀ progesterone induced decidual response (default-mg/kg)

25

30

EXAMPLE 13

5-(2,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)thiophene-2-carbonitrile

A solution of 2-amino-5-bromobenzoic acid (10g, 46 mmol) in dry THF (200 mL) was treated at -78 °C under nitrogen with a solution of methylmagnesium bromide in ether (3.0 M, 90 mL, 270 mmol). The reaction mixture was slowly warmed to ambient temperature, kept stirring for 48 hours under nitrogen and then poured into a cold 0.5 N aqueous hydrochloride solution (300 mL). The mixture was neutralized with aqueous 1 N sodium hydroxide solution and ethyl acetate (300 mL) was added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with brine and dried (MgSO_4). After removal of solvent *in vacuo*, the residue was purified by a silica gel flash column chromatography(hexane:ethyl acetate/3:2) to give 2-(2-amino-5-bromophenyl)propan-2-ol as off-white solid (6g, 57%): mp 62-63 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.19 (d, 1H, J = 2.3 Hz), 7.12 (dd, 1H, J = 8.4, 2.3 Hz), 6.51 (d, 1H, J = 8.4 Hz), 4.70 (s, 2H), 1.82 (s, 1H), 1.65 (s, 6H).

To a solution of 2-(2-amino-5-bromophenyl)propan-2-ol (27g, 125 mmol) in anhydrous toluene was added at ambient temperature under a blanket of nitrogen acetylaldehyde (10.5 mL, 187 mmol). After 10 minutes, the mixture was passed through a pad of silica gel and filtrate was concentrated to yield 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine as off-white solid (25g, 78%): $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 7.22 (d, 1H, J = 2.2 Hz), 7.08 (dd, 1H, J = 8.6, 2.3 Hz), 6.51 (d, 1H, J = 8.6 Hz), 6.36 (s, 1H), 4.72 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.25 (d, 3H, J = 5.5 Hz).

A mixture of 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine (3.6g, 14 mmol), bis(pinacolato)diboron (5 g, 19.7 mmol), potassium acetate (4g, 41 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (1:1 complex with methylene chloride, 0.4g, 0.5 mmol) in DMF (80 mL) was subject to a positive nitrogen flow to remove oxygen and then heated at 85 °C under a blanket of nitrogen for 18 hours. The mixture was allowed to cool to ambient temperature, treated with

- 60 -

5-bromo-2-thiophenecarbonitrile (4g, 21 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (1:1 complex with methylene chloride, 0.4g, 0.5 mmol), and aqueous sodium carbonate solution (2M, 35 mL, 70 mmol), and then heated at 85 °C under nitrogen for 3 hours. The reaction mixture was 5 allowed to cool to ambient temperature, brine (100 mL) and ethyl acetate (150 mL) were added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were dried (MgSO_4) and concentrated. The residue was purified by a flash silica gel column chromatography(THF:hexane/1:4) to afford the title compound as an off-white solid 10 (1g, 25%): mp 172-173 °C; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 7.88 (d, 1H, $J = 4.0$ Hz), 7.47 (d, 1H, $J = 4.0$ Hz), 7.43 (d, 1H, $J = 2.0$ Hz), 7.32 (dd, 1H, $J = 8.36, 2.4$ Hz), 6.77 (s, 1H), 6.60 (d, 1H, $J = 8.4$ Hz), 4.83 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.28 (d, 3H, $J = 5.6$ Hz); MS (ESI) m/z 283 [M-H^-].

15

EXAMPLE 14

3-Fluoro-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)benzonitrile

Prepared according to the procedure for Example 13 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 3-bromo-5-fluorobenzonitrile. A white solid: mp 163-164 °C; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 8.02 (t, 1H, $J = 1.5$ Hz), 7.87 (dt, 1H, $J = 10.6, 2.2$ Hz), 7.65 (m, 1H), 7.55 (d, 1H, $J = 2.2$ Hz), 7.44 (dd, 1H, $J = 8.4, 2.2$ Hz), 6.63 (d, 1H, $J = 8.4$ Hz), 6.58 (s, 1H), 4.82 (m, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.28 (d, 3H, $J = 5.1$ Hz); MS (ESI) m/z 295 [M-H^-].

EXAMPLE 15

4-(2,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)thiophene-2-carbonitrile

Prepared according to the procedure for Example 13 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 4-bromo-2-thiophenecarbonitrile. An off-white solid: mp 175-176 °C; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 8.39 (d, 1H, $J = 1.5$ Hz), 8.13 (d, 1H, $J = 1.5$ Hz), 7.47 (d, 1H, $J = 1.9$ Hz), 7.36 (dd, 1H, $J = 8.4, 1.9$ Hz), 6.59 (d,

- 61 -

1H, $J = 8.4$ Hz), 6.41 (s, 1H), 4.78 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.28 (d, 3H, $J = 5.4$ Hz); MS (ESI) m/z 285 [M+H]⁺.

EXAMPLE 16

5 **4-Methyl-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)thiophene-2-carbonitrile**

Prepared according to the procedure for Example 13 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 5-bromo-4-methyl-2-thiophenecarbonitrile. A yellowish solid: mp 145-146 °C; ¹H-NMR (DMSO-*d*₆) δ 7.79 (s, 1H), 7.18 (d, 1H, $J = 2.0$ Hz), 7.13 (dd, 1H, $J = 8.4, 2.0$ Hz), 6.68 (s, 1H), 6.54 (d, 1H, $J = 8.3$ Hz), 4.83 (m, 1H), 2.26 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.28 (d, 3H, $J = 5.5$ Hz); MS (ESI) m/z 299 [M+H]⁺.

EXAMPLE 17

15 **3-[(2R,4S)-2,4-Dimethyl-4-phenyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl]-5-fluorobenzonitrile**

To a solution of 2-amino-4-bromobenzonitrile (5g, 25 mmol) in anhydrous THF, was added at 0 °C under nitrogen, phenylmagnesium bromide (3 M in ether, 25 mL, 75 mmol). The mixture was allowed to warm to room temperature, stirred under nitrogen for 15 hours, and treated with 2N aqueous hydrogen chloride solution (100 mL). The aqueous solution was heated to 50 °C for 3 hours, cooled to room temperature, and neutralized with a cold saturated sodium bicarbonate solution. Ethyl acetate (100 mL) was added and the organic layer was separated and aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were dried (MgSO₄) and evaporated. The residue was purified by a flash column chromatography(silica gel, hexane:ethyl acetate/4:1) to yield (2-amino-5-bromophenyl)(phenyl)methanone as a yellow crystal (2.13g, 31%): MS (ESI) m/z 276/278 [M+H]⁺.

- 62 -

To a solution of (2-amino-5-bromophenyl)(phenyl)methanone (1g, 3.6 mmol) in anhydrous THF (15 mL) was added at room temperature under nitrogen methylmagnesium bromide (3M in ether, 3 mL, 9 mmol). After 3 hours, the mixture was treated with a saturated aqueous ammonium sulfate solution (30 mL) and ethyl acetate (50 mL). The organic layer was separated, dried (MgSO_4), and evaporated. The residue was then dissolved in anhydrous toluene and treated at ambient temperature under nitrogen with acetylaldehyde (2 mL). After 2 minutes, the solvent was removed and residue was purified by a column chromatography(silica gel, hexane:ethyl acetate/4:1) to afford 6-bromo-2,4-dimethyl-4-phenyl-1,4-dihydro-2H-3,1-benzoxazine as a yellowish solid (0.8g, 70%): MS (ESI) m/z 318/320 [M+H]⁺.

A mixture of 6-bromo-2,4-dimethyl-4-phenyl-1,4-dihydro-2H-3,1-benzoxazine (0.6g, 1.9 mmol), 3-cyano-5-fluorobenzene boronic acid (0.45g, 2.7 mmol), tetrakis(triphenylphosphine)palladium (0) (0.2g, 0.17 mmol), sodium carbonate (0.6g, 5.7 mmol) in a mixture of DME and water (20/5 mL) was subject to a positive nitrogen flow to remove oxygen and then heated to 85 °C under a blanket of nitrogen for 2 hours. The mixture was allowed to cool to ambient temperature. Brine (30 mL) and ethyl acetate (100 mL) were added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were dried (MgSO_4), and evaporated. The residue was purified by a silica gel column chromatography(hexane:ethyl acetate/4:1) to afford the title compound as off-white solid (0.09g, 13%): mp128-129 °C; ¹H-NMR (DMSO-*d*₆) δ 8.08 (s, 1H), 7.91 (dt, 1H, *J* = 10.7, 1.9 Hz), 7.71 (d, 1H, *J* = 2.0 Hz), 7.65 (m, 1H), 7.57 (dd, 1H, *J* = 8.8, 2.4 Hz), 7.32-7.36 (m, 2H), 7.24-7.29 (m, 3H), 6.71 (d, 1H, *J* = 1.6 Hz), 6.69 (d, 1H, *J* = 8.3 Hz), 4.33 (m, 1H), 1.84 (s, 3H), 1.24 (d, 3H, *J* = 5.5 Hz); MS (ESI) m/z 357 [M-H]⁻.

- 63 -

EXAMPLE 18

tert-Butyl 2-cyano-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-1-carboxylate

5 *tert*-Butyl-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-1-carboxylate was prepared according to the coupling procedure for Example 17 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 1-*t*-butoxycarbonylpyrrol-2-yl boronic acid. To a solution of *tert*-butyl-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-1-carboxylate (1g, 2.9 mmol) in anhydrous THF (20 mL) was added at -78 °C under nitrogen chlorosulfonyl isocyanate (0.35 mL, 4.0 mmol). The mixture was kept stirring at -78 °C under nitrogen for 2 hours, treated with anhydrous DMF (5 mL), and allowed to warm to room temperature. Aqueous ammonium sulfate solution (50 mL) and ethyl acetate (100 mL) was added and organic layer was separated, dried ($MgSO_4$), and evaporated.

10 The residue was purified by a silica gel column chromatography(hexane:ethyl acetate/4:1) to afford the title compound as a white solid (0.019g, 1.78%). 1H -NMR (DMSO- d_6) δ 7.48 (d, 1H, J = 2.0 Hz), 7.36 (dd, 1H, J = 8.3, 2.0 Hz), 7.32 (d, 1H, J = 3.6 Hz), 7.14 (d, 1H, J = 8.3 Hz), 6.46 (d, 1H, J = 4.0 Hz), 5.35 (q, 1H, J = 5.2 Hz), 1.58 (d, 3H, J = 5.6 Hz), 1.56 (s, 3H), 1.51 (s, 3H), 1.38 (s, 9H); MS (ESI) m/z 20 366 [M-H]⁺.

EXAMPLE 19

9H-Fluoren-9-ylmethyl-6-[1-(tert-butoxycarbonyl)-5-cyano-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate

25 A mixture of *tert*-butyl-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-1-carboxylate (1.7g, 4.96 mmol), 9-fluorenylmethyl chloroformate (1.92g, 7.5 mL), sodium carbonate (4g, 37 mmol) in dioxane (50 mL) and water (50 mL) was stirred at room temperature under a blanket of nitrogen for 6 hours. Ethyl acetate (100 mL) was added and organic layer was separated, dried ($MgSO_4$), and

evaporated. The residue was purified by a silica gel column chromatography(hexane:ethyl acetate/6:1) to afford 9H-fluoren-9-ylmethyl-6-[1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate as a clean oil.

5 Using the procedure for Example 18, the title compound (0.8g, 65%) was prepared from 9H-fluoren-9-ylmethyl-6-[1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate (1.2g, 2.1 mmol) and chlorosulfonyl isocyanate (0.28 mL, 3.1 mmol). A white solid: mp 135-136 °C; ¹H-NMR (DMSO-*d*₆) δ 7.90 (t, 2H, *J* = 6.7 Hz), 7.64 (d, 1H, *J* = 7.5 Hz), 7.59 (d, 1H, *J* = 7.1 Hz), 7.40 (td, 2H, *J* = 7.2, 2.0 Hz), 7.31-7.34 (m, 3H), 7.29 (d, 1H, *J* = 1.2 Hz), 7.04-7.09 (m, 2H), 6.44 (d, 1H, *J* = 3.57 Hz), 5.30 (q, 1H, *J* = 5.6 Hz), 4.86 (dd, 1H, *J* = 10.7, 5.2 Hz), 4.64 (dd, 1H, *J* = 10.8, 5.2 Hz), 4.33 (t, 1H, *J* = 4.7 Hz), 1.50 (s, 3H), 1.30 (s, 9H), 1.20 (s, 3H), 1.03 (d, 3H, *J* = 5.6 Hz); MS (ESI) *m/z* 590 [M+H]⁺.

15

EXAMPLE 20

5-(2,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-2-carbonitrile

9H-Fluoren-9-ylmethyl-6-[1-(tert-butoxycarbonyl)-5-cyano-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate (0.5g, 0.84 mmol) was heated 20 under a blanket of nitrogen at 160 °C until gas evolution ceased. After cooling to room temperature, 9H-fluoren-9-ylmethyl-6-[5-cyano-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate was obtained as a white solid (0.4g, 97%).

A solution of 9H-fluoren-9-ylmethyl-6-[5-cyano-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate (0.1g, 0.2 mmol) in 20% piperidine 25 in DMF (5 mL) was stirred at room temperature under nitrogen for 10 minutes. The mixture was poured into a saturated ammonium sulfate solution (30 mL) and extracted with diethyl ether (3x30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by a silica gel column chromatography(hexane:ethyl acetate/3:1) to afford the title compound as a white solid

- 65 -

(0.03g, 56%): mp 201-202 °C; ¹H-NMR (DMSO-*d*₆) δ 12.27 (s, 1H), 7.44 (d, 1H, *J* = 2.1 Hz), 7.32 (dd, 1H, *J* = 8.3, 1.1 Hz), 6.92 (dd, 1H, *J* = 4.1, 2.6 Hz), 6.57 (d, 1H, *J* = 8.3 Hz), 6.50 (dd, 1H, *J* = 4.2, 2.6 Hz), 6.40 (s, 1H), 4.77-4.80 (m, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.27 (d, 3H, *J* = 5.7 Hz); MS (ESI) *m/z* 266 [M-H]⁺.

5

EXAMPLE 21

9H-Fluoren-9-ylmethyl 6-(5-cyano-1-methyl-1H-pyrrol-2-yl)-2,4,4-trimethyl-2H-'3,1-benzoxazine-1(4H)-carboxylate

A mixture of 9H-fluoren-9-ylmethyl-6-[5-cyano-1H-pyrrol-2-yl]-2,4,4-trimethyl-2H-3,1-benzoxazine-1(4H)-carboxylate (0.4g, 0.8 mmol) and potassium carbonate (1.5g) in anhydrous DMF was treated at ambient temperature under a blanket of nitrogen with iodomethane (1.5 mL, excess). The mixture was stirred for 30 minutes. A saturated ammonium sulfate solution (50 mL) and ethyl acetate (50 mL) was added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried ($MgSO_4$), evaporated to yield the title compound as a white solid (0.35g, 87%): mp 63-64 °C; ¹H-NMR (DMSO-*d*₆) δ 7.90 (m, 2H), 7.62 (d, 1H, *J* = 7.7 Hz), 7.58 (d, 1H, *J* = 7.7 Hz), 7.40 (m, 2H), 7.29-7.32 (m, 3H), 7.14 (dd, 1H, *J* = 8.1, 1.9 Hz), 7.01-7.04 (m, 2H), 6.33 (d, 1H, *J* = 4.3 Hz), 5.31 (q, 1H, *J* = 5.8 Hz), 4.88 (dd, 1H, *J* = 10.8, 5.0 Hz), 4.65 (dd, 1H, *J* = 10.8, 4.6 Hz), 4.34 (t, 1H, *J* = 4.6 Hz), 3.71 (s, 3H), 1.52 (s, 3H), 1.21 (s, 3H), 1.06 (d, 3H, *J* = 5.4 Hz); MS (ESI) *m/z* 504 [M+H]⁺.

EXAMPLE 22

1-Methyl-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-2-carbonitrile

25

Prepared according to the procedure for Example 20 from 9H-fluoren-9-ylmethyl 6-(5-cyano-1-methyl-1H-pyrrol-2-yl)-2,4,4-trimethyl-2H-'3,1-benzoxazine-1(4H)-carboxylate (0.3g, 0.6 mmol) and 20% piperidine in DMF. A white solid

- 66 -

(0.07g, 42%): mp 195-196 °C; ¹H-NMR (DMSO-*d*₆) δ 7.16 (d, 1H, *J* = 2.8 Hz), 7.08 (dd, 1H, *J* = 8.1, 1.9 Hz), 6.98 (d, 1H, *J* = 4.1 Hz), 6.63 (d, 1H, *J* = 8.5 Hz), 6.61 (s, 1H), 6.20 (d, 1H, *J* = 4.1 Hz), 4.79-4.81 (m, 1H), 3.67 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.27 (d, 3H, *J* = 5.5 Hz); MS (ESI) *m/z* 282 [M+H]⁺.

5

EXAMPLE 23

5-(2-Methylspiro[4H-3,1-benzoxazine-4,1'-cyclopentane]-6-yl)-4-methyl-2-thiophenecarbonitrile

2-Methyl-6-bromospiro[4H-3,1-benzoxazine-4,1'-cyclopentane] was prepared
10 using the same procedure as for 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine in Example 13.

The title compound was prepared according to the procedure for Example 13 from 2-methyl-6-bromospiro[4H-3,1-benzoxazine-4,1'-cyclopentane] and 5-bromo-4-methyl-2-thiophenecarbonitrile. A yellowish solid: mp 58-60 °C; ¹H-NMR (DMSO-*d*₆) δ 7.79 (s, 1H), 7.16 (d, 1H, *J* = 1.9 Hz), 7.12 (dd, 1H, *J* = 8.4, 2.2 Hz), 6.66 (s, 1H), 6.63 (d, 1H, *J* = 8.4 Hz), 4.75 (m, 1H), 2.26 (s, 3H), 2.14 (m, 1H), 1.87 (m, 1H), 1.4-1.7 (m, 6H), 1.32 (d, 3H, *J* = 5.5 Hz).

EXAMPLE 24

4-(2-Methylspiro[2H-3,1-benzoxazine-4,1'-cyclopentane]-6-yl)-2-thiophenecarbonitrile

Prepared according to the procedure for Example 13 from 2-methyl-6-bromospiro[4H-3,1-benzoxazine-4,1'-cyclopentane] and 4-bromo-2-thiophenecarbonitrile. An off-white solid: mp 103-104 °C.

25

- 67 -

EXAMPLE 25

5-(2-methylspiro[2H-3,1-benzoxazine-4,1'-cyclohexane]-6-yl)-4-methyl-2-thiophenecarbonitrile

5 2-Methyl-6-bromospiro[2H-3,1-benzoxazine-4,1'-cyclohexane] was prepared using the same procedure as for 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine in Example 13.

The title compound was prepared according to the procedure for Example 13 from 2-methyl-6-bromospiro[4H-3,1-benzoxazine-4,1'-cyclohexane] and 5-bromo-4-methyl-2-thiophenecarbonitrile. A brown solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 7.78 (s, 1H), 7.17 (d, 1H, J = 1.8 Hz), 7.14 (dd, 1H, J = 8.4, 2.2 Hz), 6.64 (s, 1H), 6.63 (d, 1H, J = 8.2 Hz), 4.74 (m, 1H), 2.26 (s, 3H), 2.14 (m, 1H), 1.87 (m, 1H), 1.4-1.7 (m, 8H), 1.31 (d, 3H, J = 5.3 Hz); MS (ESI) m/z 337 [M-H] $^+$.

15

EXAMPLE 26

4-(2-Methylspiro[2H-3,1-benzoxazine-4,1'-cyclohexane]-6-yl)2-thiophenecarbonitrile

Prepared according to the procedure for Example 13 from 2-methyl-6-bromospiro[4H-3,1-benzoxazine-4,1'-cyclohexane] and 4-bromo-2-thiophenecarbonitrile. A brown solid: mp 111-112 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 8.42 (s, 1H), 8.14 (s, 1H), 7.47 (s, 1H), 7.35 (dd, 1H, J = 8.3, 1.1 Hz), 6.58 (d, 1H, J = 8.4 Hz), 6.38 (s, 1H), 4.72 (m, 1H), 1.92-2.16 (m, 2H), 1.35-1.75 (m, 8H), 1.31 (d, 3H, J = 5.3 Hz); MS (ESI) m/z 325 [M+H] $^+$.

25

EXAMPLE 27

6-(3-Fluorophenyl)-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine

Prepared according to the coupling procedure for Example 17 from 3-fluorophenyl boronic acid and 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-

- 68 -

benzoxazine. A yellow solid: mp 139-140°C; ¹H-NMR (CDCl₃) δ 7.40-7.19 (m, 6H), 7.01-6.94 (m, 1H), 6.72 (d, 1H, J = 8.24 Hz), 4.90 (q, 1H, J = 5.48 Hz), 1.62 (s, 3H), 1.59 (s, 3H), 1.46 (d, 3H, J = 5.5 Hz); MS (ES) m/z 272 ([M+H]⁺).

5

EXAMPLE 28

6-(3-Chlorophenyl)-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine

Prepared according to the coupling procedure for Example 17 from 3-chlorophenyl boronic acid and 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine. A orange solid: mp 144-146 °C; ¹H-NMR (CDCl₃) δ 7.50 (t, 1H, J = 1.78 Hz), 7.40 (dt, 1H, J = 7.61, 1.45 Hz), 7.33 (t, 1H, J = 7.76 Hz), 7.29-7.22 (m, 4H) 6.72 (d, 1H, J = 8.24 Hz), 4.90 (q, 1H, J = 5.45 Hz), 1.62 (s, 3H), 1.59 (s, 3H), 1.46 (d, 3H, J = 5.5 Hz); MS (ES) m/z 288/290 ([M + H]⁺).

15

EXAMPLE 29

6-(3-Chloro-4-fluorophenyl)-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine

A mixture of 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine (3.0 g, 11.7 mmol), 3-chloro-4-fluorobenzeneboronic acid (3.1 g, 17.6 mmol), tetrakis(triphenylphosphine)palladium (0) (0.67 g, 0.59 mmol), and sodium carbonate (3.72 g, 35.1 mmol) in DME (80 mL) and water (40 mL) was subject to a blanket of nitrogen flow for 15 minutes at 50°C and then was heated at 85°C under nitrogen for 1 hour. The reaction was cooled to room temperature and ethyl acetate (200 mL) was added. The organic layer was washed twice with aqueous ammonium chloride (50 mL) and once with brine (50 mL), dried over sodium sulfate and concentrated to a yellow solid. The solid was triturated with ether (25 mL) and hexane (25 mL), collected on a filter, and dried to give 6-(3-chloro-4-fluorophenyl)-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine (1.87 g, 35%) as a yellow solid: mp 173-175°C; ¹H-NMR (DMSO-d₆) δ 7.79 (dd, 1H, J = 6.84, 2.14 Hz), 7.60-7.57 (m, 1H), 7.43-7.39 (m, 2H), 7.29 (dd, 1H, J = 8.12, 2.14 Hz), 6.62 (d, 1H, J = 8.54 Hz), 6.40 (s, 1H),

- 69 -

4.79 (q, 1H, $J = 5.55$ Hz), 1.53 (s, 3H), 1.48 (s, 3H), 1.28 (d, 3H, $J = 5.55$ Hz); MS (ES) m/z 306/308([M + H]⁺).

EXAMPLE 30

5 **2-Fluoro-5-(2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)benzonitrile**

Prepared according to the coupling procedure for Example 13 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 5-bromo-2-fluorobenzonitrile. A white solid: mp 184-186°C; ¹H-NMR (DMSO-*d*₆) δ 8.17 (dd, 1H, $J = 5.86, 3.42$ Hz), 8.00-7.98 (m, 1H), 7.52 (t, 1H, $J = 9.28$ Hz), 7.45 (d, 1H, $J = 1.95$ Hz), 7.34 (dd, 1H, $J = 8.30, 1.95$ Hz), 6.63 (d, 1H, $J = 8.3$ Hz), 6.45 (d, 1H), 4.8 (q, 1H, $J = 5.37$ Hz), 1.53 (s, 3H), 1.49 (s, 3H), 1.29 (d, 3H, $J = 5.37$ Hz); MS (ES) m/z 297 ([M + H]⁺).

EXAMPLE 31

15 **4-(2,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-2-furonitrile**

Prepared using the coupling procedure for Example 13 from 6-bromo-2,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine and 4-bromo-2-cyanofuran. A light brown solid: mp 116-118 °C; ¹H-NMR (DMSO-*d*₆) δ 8.43 (s, 1H), 8.06 (s, 1H), 7.38 (d, 1H, $J = 1.98$ Hz), 7.25 (dd, 1H, $J = 7.93, 1.98$ Hz) 6.58 (d, 1H, $J = 7.93$ Hz), 6.37 (s, 1H), 4.77 (q, 1H, $J = 5.55$ Hz), 1.50 (s, 3H), 1.46 (s, 3H), 1.27 (d, 3H, $J = 5.55$ Hz); MS (ES) m/z 269 ([M+H]⁺); Anal. Calc. For C₁₆H₁₆N₂O₂: C, 71.62; H, 6.01, N, 10.44. Found: C, 71.55; H, 6.26, N, 10.17.

EXAMPLE 32

25 **3-[4,4-Dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-yl]-5-fluorobenzonitrile**

A mixture of 2-(2-amino-5-bromo-phenyl)-propan-2-ol (5 g, 21.7 mmol), trifluoroacetaldehyde methyl hemiacetal (5 mL), and magnesium sulfate (10 g) in toluene (75 mL) was heated at 80°C under nitrogen. After disappearance of the starting material, the reaction was filtered through a pad of silica gel and the filtrate

- 70 -

dried over sodium sulfate and concentrated to give 6-bromo-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine as an amorphous solid: ¹H-NMR (DMSO-*d*₆) δ 7.31 (d, 1H, *J* = 1.99 Hz), 7.19 (dd, 1H, *J* = 8.73, 2.38 Hz), 6.88 (s 1H), 6.74 (d, 1H, *J* = 8.33 Hz), 5.32 (m, 1H), 1.52 (s, 6H).

5 A mixture of 6-bromo-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine (0.5 g, 1.61 mmol), 3-cyano-5-fluorobenzeneboronic acid (0.39 g, 1.8 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.2 g, 0.161 mmol), and sodium carbonate (0.5 g, 4.83 mmol) in DME (50 mL) and water (25 mL) was subject to a blanket of nitrogen flow for 15 minutes at 50°C and then was heated at 85°C under
10 nitrogen for 1 hour. The reaction mixture was cooled to room temperature and ethyl acetate (200 mL) was added. The organic layer was washed twice with aqueous ammonium chloride (20 mL) and once with brine (20 mL), dried over sodium sulfate and concentrated to a yellow solid. Purification via flash column chromatography (silica gel, 5% ethyl acetate/hexane) gave 3-[4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-yl]-5-fluorobenzonitrile (0.396 g, 73%) as a white solid:
15 mp 102-103°C; ¹H-NMR (DMSO-*d*₆) δ 8.07 (s, 1H), 7.91 (d, 1H, *J* = 10.7 Hz), 7.7 (d, 1H, *J* = 10.7 Hz) 7.62 (d, 1H, *J* = 1.98 Hz), 7.53 (dd, 1H, *J* = 8.33, 1.98 Hz), 7.05 (s, 1H), 6.87 (d, 1H, *J* = 8.33 Hz), 5.39-5.37 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H); MS (ES) *m/z* 349 ([M-H]⁺).

20

EXAMPLE 33

4-[4,4-Dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-yl]thiophene-2-carbonitrile

Prepared using the coupling procedure for Example 13 starting with 6-bromo-
25 4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine and 4-bromo-2-thiophenecarbonitrile. A yellow solid: ¹H-NMR (DMSO-*d*₆) δ 8.43 (s, 1H), 8.19 (s, 1H), 7.54 (d, 1H, *J* = 1.98 Hz), 7.46 (dd, 1H, *J* = 8.33, 1.98 Hz), 6.90 (s, 1H), 6.83 (d, 1H, *J* = 8.33 Hz), 5.35 (d, 1H, *J* = 3.57 Hz), 1.59 (s, 3H), 1.57 (s, 3H); MS (ES) *m/z* 337 ([M-H]⁺).

- 71 -

EXAMPLE 34

4-[1-Acetyl-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-yl]thiophene-2-carbonitrile

5 4-[4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-
yl]thiophene-2-carbonitrile (0.25 g, 0.74 mmol) was dissolved in DMF (10 mL), NaH
(0.09 g, 2.22 mmol) was added and the mixture was stirred for 30 minutes prior to the
addition of acetyl chloride (0.079 mL, 1.11 mmol). Upon disappearance of the starting
material the reaction mixture was poured into brine (100 mL) and the product
10 extracted with ether (150 mL), dried over sodium sulfate and concentrated. The
residue was purified by a flash column chromatography (silica gel, 25% ethyl
acetate/hexane) to yield 4-[1-acetyl-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-
3,1-benzoxazin-6-yl]thiophene-2-carbonitrile (0.1 g, 36%) as an amorphous solid: ¹H-NMR (DMSO-*d*₆) δ 8.58 (s, 1H), 8.5 (s, 1H), 7.83-7.80 (m, 2H), 7.64 (d, 1H, *J* =
15 8.74 Hz), 6.42 (q, 1H, *J* = 10 Hz), 2.24 (s, 3H), 1.73 (s, 3H), 1.42 (s, 3H).

EXAMPLE 35

(6(5-Cyanothien-3-yl)-4,4-dimethyl-2-(trifluoromethyl)-2H-3,1-benzoxazin-1(4H)-yl)methyl pivalate

20 4-[4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-
yl]thiophene-2-carbonitrile (0.30 g, 0.89 mmol) was dissolved in DMF (10 mL), NaH
(0.065 g, 2.7 mmol) was added and the was mixture stirred for 30 minutes prior to the
addition of *tert*-butyl chloroacetate (0.19 mL, 1.3 mmol). Upon disappearance of the
starting material the reaction mixture was poured into brine (100 mL) and the product
25 extracted with ether (150 mL), dried over sodium sulfate and concentrated. Flash
column chromatography (silica gel, 8% ethyl acetate/hexane) gave (6(5-cyanothien-3-
yl)-4,4-dimethyl-2-(trifluoromethyl)-2H-3,1-benzoxazin-1(4H)-yl)methyl pivalate
(0.127 g, 32%) as an amorphous solid: ¹H-NMR (CDCl₃) δ 7.82 (s, 1H), 7.58 (s, 1H),
7.41 (dd, 1H, *J* = 8.33, 1.98 Hz), 7.25 (d, 1H, *J* = 1.98 Hz) 7.10 (d, 1H, *J* = 8.33 Hz),

- 72 -

6.79 (d, 1H, $J = 8.33$ Hz), 5.66 (d, 1H, $J = 11.9$ Hz), 5.38 (d, 1H, $J = 11.9$ Hz), 1.72 (s, 3H), 1.55 (s, 3H), 1.18 (s, 9H).

EXAMPLE 36

5 **3-Fluoro-5-(2,2,4,4-tetramethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)benzonitrile**

Prepared using the coupling procedure for Example 13 starting with 6-bromo-2,2,4,4-tetramethyl-1,4-dihydro-2H-3,1-benzoxazine and 3-bromo-5-fluorobenzonitrile. A white solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 8.03 (s, 1H), 7.87 (d, 1H, $J = 10.7$ Hz), 7.65 (d, 1H, $J = 10.7$ Hz), 7.57 (d, 1H, $J = 1.98$ Hz) 7.45 (dd, 1H, $J = 8.33, 1.98$ Hz), 6.65 (d, 1H, $J = 8.33$ Hz), 6.42 (s, 1H), 1.52 (s, 6H), 1.34 (s, 6H); MS (ES) m/z 311 ($[\text{M}+\text{H}]^+$).

EXAMPLE 37

15 **4-(2,2,4,4-Tetramethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)thiophene-2-carbonitrile**

Prepared using the coupling procedure for Example 13 starting with 6-bromo-2,2,4,4-tetramethyl-1,4-dihydro-2H-3,1-benzoxazine and 4-bromo-2-cyanothiophene. An amorphous orange solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 8.4 (d, 1H, $J = 1.69$ Hz), 8.14 (d, 1H, $J = 1.69$ Hz), 7.49 (d, 1H, $J = 2.20$ Hz), 7.38 (dd, 1H, $J = 8.43, 2.02$ Hz), 6.61 (d, 1H, $J = 8.43$ Hz), 6.26 (s, 1H), 1.49 (s, 6H), 1.32 (s, 6H); MS (ES) m/z 299 ($[\text{M}+\text{H}]^+$).

EXAMPLE 38

25 **5-[4,4-Dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-6-yl]-4-methylthiophene-2-carbonitrile**

Prepared according to the coupling procedure for Example 13 from 6-bromo-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine and 5-bromo-4-methyl-2-thiophene-carbonitrile. A yellowish solid: mp 97-98 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 7.82 (s, 1H), 7.26 (d, 1H, $J = 1.7$ Hz), 7.21 (dd, 1H, $J = 8.1, 2.1$ Hz), 7.16 (s,

- 73 -

1H), 6.88 (d, 1H, $J = 8.1$ Hz), 5.40 (m, 1H), 2.27 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H);
MS (ESI) m/z 351 [M-H]⁻.

EXAMPLE 39

5 **6-(3-Chlorophenyl)-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine**

Prepared according to the coupling procedure for Example 17 from 6-bromo-4,4-dimethyl-2-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine and 3-chlorophenyl boronic acid. A yellowish solid: mp 108-109 °C; ¹H-NMR (DMSO-*d*₆) δ 7.69 (t, 1H, $J = 1.7$ Hz), 7.59 (d, 1H, $J = 7.8$ Hz), 7.35-7.50 (m, 3H), 7.32 (dt, 1H, $J = 8.1, 1.1$ Hz), 6.91 (s, 1H), 6.87 (d, 1H, $J = 8.4$ Hz), 5.35 (m, 1H), 1.60 (s, 3H), 1.59 (s, 3H);
MS (ESI) m/z 340 [M-H]⁻.

EXAMPLE 40

15 **6-(3-Fluorophenyl)-4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one**

Prepared by coupling 3-fluorophenylboronic acid with an equivalent amount of 6-bromo-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one using a catalytic amount of tetrakis(triphenylphosphine)palladium(0) with overnight refluxing in toluene containing an equivalent amount of potassium carbonate dissolved in water. Work up in the usual manner followed by recrystallization from ethanol gave a grey solid: mp 190-192°C.
¹H-NMR (DMSO-*d*₆) δ 10.27 (s, 1H), 7.57 (s, 1H), 7.50 (m, 4H), 7.15 (m, 1H), 6.95 (d, 1H $J = 8.2$ Hz), 2.39 (s, 2H), 1.29 (s, 6H); MS (APCI (-)) m/z 268 [M-H]⁻ Anal. Calc. For C₁₇H₁₆FNO 0.25 H₂O: C, 74.57, H, 6.07, N, 5.12. Found: C, 74.86, H, 5.97, N 5.06.

- 74 -

EXAMPLE 41

3-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-5-fluorobenzonitrile

6-bromo-4,4-quinolin-2-one was allowed to couple with an equivalent of bis(pinacolato)diboron in refluxing DMF containing an equivalent of sodium carbonate dissolved in a minimal amount of water and a catalytic quantity of tetrakis(triphenylphosphine)palladium(0). After refluxing overnight an equivalent of 3-bromo-5-fluorobenzonitrile was added. Another equivalent of sodium carbonate was then added, followed by an additional amount of the same catalyst. After several hours of reflux, the reaction mixture was filtered and taken to dryness *in vacuo*. The residue was extracted into ethyl acetate and the solution was dried over magnesium sulfate, filtered and the filtrate was again roto-evaporated to give a solid residue. Recrystallization from ethanol afforded the title compound as a grey solid: mp 249-250° C. ¹H-NMR (DMSO-*d*₆) δ 10.32 (s, 1H), 8.09 (t, 1H, *J* = 1.6Hz), 7.93 (d, 1H, *J* = 12.7 Hz) 7.77, (d, 1H, *J* = 8.1Hz), 7.70 (s, 1H), 7.61(d, 1H *J* = 8.9Hz), 6.95 (d, 1H, *J* = 8.3Hz), 2.40 (s, 2H), 1.30 (s, 6H); MS (APCI (-)) *m/z* 293 [M-H]⁻ Anal. Calc. For C₁₈H₁₅FN₂O 1.5H₂O : C, 67.28, H, 5.65, N, 8.72. Found: C, 67.36, H, 4.90, N 8.44..

- 75 -

EXAMPLE 42

3-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)benzonitrile

Prepared by coupling 3-cyanophenylboronic acid with an equivalent amount of 5 6-bromo-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one using a catalytic amount of tetrakis(triphenylphosphine)palladium(0) as a catalyst with overnight refluxing in toluene containing an equivalent amount of potassium carbonate dissolved in water in the usual manner followed by recrystallization from ethanol gave a grey solid: mp. 190 – 192 °C; ¹H-NMR (DMSO-*d*₆) δ 10.29 (s, 1H), 8.17 (s, 1H), 8.00 (d, 1H, J = 7.9 Hz), 7.77 (d, 1H, J = 6.4Hz), 7.65 (m, 2H), 7.55 (d, 1H, J = 8.2 Hz), 6.97 (d, 1H, J = 8.3 Hz), 2.40 (s, 2H), 1.30 (s, 6H); MS (APCI (-)) m/z 275 [M-H]⁺ Anal. Calc. For C₁₈H₁₆N₂O 0.25H₂O: C, 75.77, H, 6.01, N, 9.82. Found: C, 75.45, H, 5.65, N 9.20.

EXAMPLE 43

6-(3-Chlorophenyl)-4,4-dimethyl-3,4-dihydroquinoline-2(1H)-thione

Prepared by heating under reflux overnight a mixture of 6-(3-chlorophenyl)-4,4-dimethyl-3,4-dihydroquinoline-2(1H)-one and an equal weight of phosphorus pentasulfide in pyridine was stirred. Removal of the pyridine *in vacuo* followed by treating the residue with 6N hydrochloric acid and recrystallization of the residue in 20 ethanol gave the product as a yellow solid: mp. 197 - 198°C. ¹H-NMR (DMSO-*d*₆) δ 12.34 (s, 1H), 7.75 (m, 1H), 7.64 (m, 2H), 7.57 (dd, 1H J= 9.3 and 2.1 Hz), 7.48 (t, 1H, J = 7.7 Hz), 7.41 (m, 1H), 7.20 (d, 1H, J = 8.3 Hz), 3.34 (s, 2H), 1.26 (s, 6H); MS (APCI (-)) m/z 300 [M-H]⁺ Anal. Calc. For C₁₇H₁₆ClNS: C, 67.65, H, 5.34, N, 4.64. Found: C, 67.77, H, 5.57, N 4.54.

- 76 -

EXAMPLE 44

6-(3-Fluorophenyl)-4,4-dimethyl-3,4-dihydroquinoline-2(1H)-thione

Prepared by heating under reflux overnight a mixture of 6-(3-fluorophenyl)-4,4-dimethyl-3,4-dihydroquinoline-2(1H)-one and an equal weight of phosphorus pentasulfide was stirred in pyridine. Workup as in the previous example gave a yellow solid, mp 209-211° C. ¹H-NMR (DMSO-*d*₆) δ 12.34 (s, 1H), 7.65 (d, 1H, *J*=2.2 Hz) 7.57 (dd, 1H, *J*₁=8.24, *J*₂=2.2Hz), 7.51(m,3H), 7.18(m,2H), 2.84(s,2H), 1.26(s,6H). MS *m/z* 284 [M-H]⁻ Anal. Calc. For C₁₇H₁₆F₁NS: C, 71.55, H, 5.65, N, 4.91. Found: C, 71.18, H, 5.59, N, 4.82.

10

EXAMPLE 45

3-(4,4-Dimethyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-yl)benzonitrile

Prepared by heating under reflux overnight a stirred mixture of 3-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)benzonitrile and an equal weight of phosphorus pentasulfide in pyridine and workup as in the previous example gave a yellow solid: mp 220-223 °C dec. ¹H-NMR (DMSO-*d*₆) δ 12.35 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*= 6.0 Hz), 7.80 (d, 1H, *J*= 7.9Hz), 7.72 (s, 1H), 7.65 (m, 2H), 7.21 (d, 1H, *J*= 8.4 Hz), 2.85 (s, 2H), 1.27 (s, 6H); MS (APCI (-)) *m/z* 291 [M-H]⁻ Anal. Calc. For C₁₈H₁₆N₂S 3H₂O: C, 62.40, H, 6.40, N, 8.09. Found: C, 62.12, H, 4.88, N 20 7.77.

EXAMPLE 46

3-(4,4-Dimethyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-yl)-5-fluorobenzonitrile

Prepared by heating under reflux overnight a stirred mixture of 3-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-5-fluorobenzonitrile and an equal weight of phosphorus pentasulfide in pyridine and workup as in the previous example gave a yellow solid: mp. 240-242° C dec.; ¹H-NMR (DMSO-*d*₆) δ 12.37 (s, 1H), 8.13 (s, 1H), 7.98 (dt, 1H, *J*= 10.4 and 5.4 Hz), 7.81 (d, 1H, *J*= 8.4Hz), 7.7 (d, 1H, *J*=

- 77 -

1.8Hz), 7.68 (dd, 1H, J = 8.3 and 1.9 Hz), 7.22 (d, 1H, J = 8.3Hz), 2.85 (s, 2H), 1.27 (s, 6H); MS m/z 309 [M-H]⁺ Anal. Calc. For C₁₈H₁₅FN₂S 0.10 H₂O: C, 69.25, H, 4.91, N, 8.97. Found: C, 69.15, H, 4.74, N 8.75.

5

EXAMPLE 47

6-(3-Fluoro-phenyl)-2,4,4-trimethyl-1,2,3,4-tetrahydro-quinoline

6-Bromo-1-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one.

To a solution of 6-bromo-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (0.5g, 1.97mmol) in THF (25mL) was added 60% NaH (0.12g, 2.95mmol) suspended in mineral oil. The resulting reaction mixture was stirred at room temperature for 30 min., 4-methoxybenzyl chloride (0.34g, 2.17) added, and heated under reflux for 20 h. The reaction was cooled to room temperature then quenched slowly with water. After extraction with ethyl acetate, the organic layer was dried (MgSO₄), evaporated and the residue purified by chromatography (SiO₂ 3:7 ethyl acetate/hexane). The white crystalline product was obtained (0.35g, 48%); mp 118-119 °C, ¹H NMR (DMSO-d₆) δ 1.23 (s, 6H), 2.59 (s, 2H), 3.70 (s, 3H), 3.72 (s, 1H), 4.41 (d, 1H, J = 5.86Hz), 5.09 (s, 1H), 6.87 (m, 2H), 7.01 (d, 1H, J = 8.78Hz), 7.17 (d, 1H, J = 8.98Hz), 7.23 (d, 1H, J = 8.79), 7.34 (dd, 1H, J = 6.59 and 2.2 Hz), 7.43(d, 1H, J = 2.2Hz); MS (APCI (+)) [M+H]⁺ =374/376.

20 **6-(3-Fluoro-phenyl)-1-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one.**

A mixture of 6-Bromo-1-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (2.9g, 7.75mmol) in ethylene glycol dimethyl ether (50mL), K₂CO₃ (1.18 g, 8.53mmol) in H₂O (5.0mL), and a catalytic amount of tetrakis(triphenylphosphine) palladium was heated under reflux overnight. After cooling to room temperature, the mixture was extracted with ethyl acetate and the organic phase was washed with NaHCO₃ solution, brine, dried over MgSO₄, concentrated, and crystallized from ethanol to obtain the product as a white crystalline material (1.8 g, 60%): mp 159 – 162 °C, ¹H NMR (DMSO-d₆) δ 1.32 (s, 6H), 2.63 (s, 2H), 3.70 (s,

3H), 5.15 (s, 2H), 6.89 (d, 2H, $J = 11.72\text{Hz}$), 7.14 (m, 2H), 7.22 (d, 2H, $J = 8.8\text{Hz}$),
7.53 (m, 4H), 7.60 (d, 1H, $J = 2.2\text{Hz}$); MS (APCI (+)) $[\text{M}+\text{H}]^+ = 390$.

6-Bromo-1-(4-methoxy-benzyl)-2,4,4-trimethyl-1,4-dihydro-quinoline.

To a solution of 6-(3-Fluoro-phenyl)-1-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (1.16g, 2.99mmol) in THF (15mL) at room temperature was added a solution of 1.4 M MeMgBr (2.6mL, 12.56mmol) and the resulting reaction mixture was stirred for 6h. The solution was quenched with H_2O , extracted with EtOAc, treated with ammonium chloride solution, washed with brine, dried over MgSO_4 , and concentrated. The product was purified by column chromatography using a 2:8 hexane/ethyl acetate mixture and used below.

To a solution of 6-(3-Fluoro-phenyl)-1-(4-methoxy-benzyl)-2,4,4-trimethyl-1,2,3,4-tetrahydroquinoline (0.15g, 0.39mmol) in EtOH (35mL) was added 10%Pd/C and hydrogenated for 10 h at 40 psi. The catalyst was removed by filtration through celite and the product purified by chromatography. A reddish liquid was obtained. ^1H NMR ($\text{DMSO}-d_6$) δ 1.15 (d, 3H, $J = 6.73\text{Hz}$), 1.21(s, 3H), 1.34(m, 4H), 1.60(dd, 1H, $J_1 = 10.1, J_2 = 2.69, \text{Hz}$), 3.40(m, 1H), 5.95(s, 1H), 6.55(d, 1H, $J = 8.08\text{Hz}$), 7.01(m, 1H), 7.21(dd, 1H, $J_1 = 5.78, J_2 = 2.02 \text{ Hz}$), 7.35(m,4H); MS(FI Pos) $[\text{M}+\text{H}]^+ = 270$.

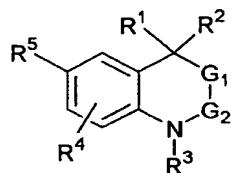
Still other compounds, including 5-(2,4,4-Trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-1H-pyrrole-2-carbonitrile, 1-Methyl-5-(2,4,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-1H-pyrrole-2- carbonitrile , and 3-Fluoro-5-(2,4,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-benzonitrile may be prepared using the methods described above.

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

- a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of Formula I:



I

wherein:

R¹, R² are independent substituents selected from the group which includes H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R¹ and R² are fused to form:

- a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring;
- b) an optionally substituted 3 to 8 membered spirocyclic alkenyl; or
- c) an optionally substituted 3 to 8 membered heterocyclic ring containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings of a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

- 80 -

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl,

R^B is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl,

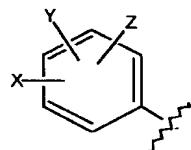
R^3 is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C,

R^C is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl,

R^4 is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, alkynyl, or substituted alkynyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl,

R^5 is selected from a) or b):

a) R^5 is a trisubstituted benzene of the structure:



X is taken from the group including halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, alkynyl, or substituted alkynyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D,

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, amino, aminoalkyl, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy; or

b) R⁵ is a five or six membered ring with 1, 2, or 3 heteroatoms selected from O, S, SO, SO₂ or NR⁶ and containing one or two independent substituents selected from H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^G is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R⁶ is H or C₁ to C₃ alkyl;

G₁ is O, NR₇, or CR₇R₈;

G₂ is CO or CR₇R₈; provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

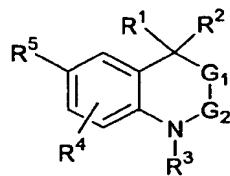
R₇ and R₈ are independently selected from H or an optionally substituted alkyl, aryl, or heterocyclic moiety;

or pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:

- 82 -



I

wherein:

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , or NR^BCOR^A ;

R^2 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , or NR^BCOR^A ;

or

R^1 and R^2 are fused to form an optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic ring containing one to three heteroatoms from the group including O, S and N, the spirocyclic alkyl, alkenyl or heterocyclic rings being optionally substituted by from 1 to 4 groups selected from fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 thioalkyl, $-CF_3$, $-OH$, $-CN$, NH_2 , $-NH(C_1$ to C_6 alkyl), or $-N(C_1$ to C_6 alkyl) $_2$;

R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl,

- 83 -

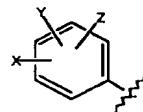
R^3 is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R^4 is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl,

R^5 is a) or b):

a) R⁵ is a benzene ring of the structure:



X is selected from halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

or

b) R⁵ is a five or six membered ring with 1, 2, or 3 heteroatoms selected from the group of O, S, SO, SO₂ or NR⁶ and containing one or two independent substituents selected from H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, C₁ to C₃ alkoxy;

R⁶ is H, or C₁ to C₃ alkyl.

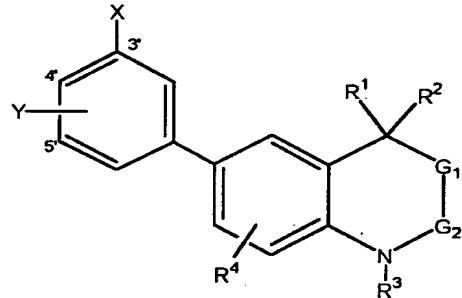
G₁ is O, NR₇, or CR₇R₈

G₂ is CO or CR₇R₈; provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

R₇ and R₈ are independently selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic;

or a pharmaceutically acceptable salt thereof.

3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

$R^1 = R^2$ and are selected from C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring, the spirocyclic ring being optionally substituted by from 1 to 4 groups selected from fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 thioalkyl, $-CF_3$, $-OH$, $-CN$, NH_2 , $-NH(C_1$ to C_6 alkyl), or $-N(C_1$ to C_6 alkyl) $_2$;

R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, $-COH$, $-CO(C_1$ to C_4 alkyl) or $-CO(C_1$ to C_4 alkoxy);

R^4 is H, halogen, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl;

X is taken from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, C_1 to C_3 thioalkoxy,

Y is a substituent on the 4' or 5' position from the group including H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, C_1 to C_3 thioalkoxy

G_1 is O, NR_7 , or CR_7R_8

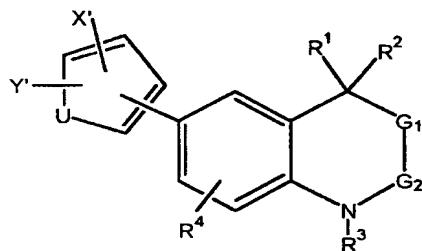
- 86 -

G_2 is CO or CR_7R_8 ; provided that when G_1 is O, G_2 is CR_7R_8 , and G_1 and G_2 cannot both be CR_7R_8 ;

wherein R_7 and R_8 are independent substituents selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic;

or pharmaceutically acceptable salt thereof

4. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

$R^1 = R^2$ and are selected from C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring, the spirocyclic ring being optionally substituted by from 1 to 4 groups selected from fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 thioalkyl, $-CF_3$, $-OH$, $-CN$, NH_2 , $-NH(C_1$ to C_6 alkyl), or $-N(C_1$ to C_6 alkyl) $_2$;

R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, $-COH$, $-CO(C_1$ to C_4 alkyl) or $-CO(C_1$ to C_4 alkoxy);

R^4 is H, halogen, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl;

- 87 -

U is O, S, or NR⁶,

R⁶ is H, or C₁ to C₃ alkyl, C₁ to C₄ CO₂alkyl,

X' is from the group including halogen, CN, NO₂, C₁ to C₃ alkyl and C₁ to C₃ alkoxy;

Y' is from the group including H and C₁ to C₄ alkyl;

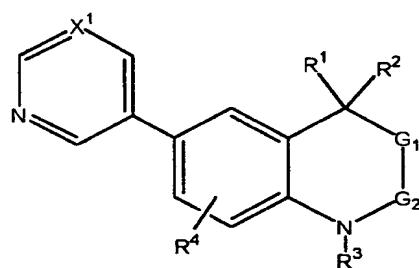
G₁ is O, NR₇, or CR₇R₈;

G₂ is CO or CR₇R₈; provided that when G₁ is O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈;

wherein R₇ and R₈ are independent substituents selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic;

or pharmaceutically acceptable salt thereof

5. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

$R^1 = R^2$ and are selected from C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring, the spirocyclic rings of being optionally substituted by from 1 to 4 groups selected from fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 thioalkyl, $-CF_3$, $-OH$, $-CN$, NH_2 , $-NH(C_1$ to C_6 alkyl), or $-N(C_1$ to C_6 alkyl) $_2$;

R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, $-COH$, $-CO(C_1$ to C_4 alkyl) or $-CO(C_1$ to C_4 alkoxy);

R^4 is H, halogen, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl;

X^1 is N or CX^2 ,

X^2 is halogen, CN, alkoxy, or NO_2 ,

G_1 is O, NR_7 , or CR_7R_8

G_2 is CO or CR_7R_8 ; provided that when G_1 is O, G_2 is CR_7R_8 , and G_1 and G_2 cannot both be CR_7R_8 ;

wherein R_7 and R_8 are independent substituents selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic;

or pharmaceutically acceptable salt thereof

6. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chloro-phenyl)-2,4,4-trimethyl-2-trifluoromethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine or a pharmaceutically acceptable salt thereof.

7. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chloro-phenyl)-2,2,4,4-tetramethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine or a pharmaceutically acceptable salt thereof.

8. A method of Claim 1 in which the antiprogestin compound is 6-(3-Nitro-phenyl)-2,2,4,-trimethyl-1,4-dihydro-2H-benzo[d][1,3]oxazine or a pharmaceutically acceptable salt thereof.

9. A method of Claim 1 in which the antiprogestin compound is 4-Amino-3'-chloro-biphenyl-3-carbonitrile or a pharmaceutically acceptable salt thereof.

10. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chlorophenyl)-4-cyclopropyl-1H-quinazolin-2-one or a pharmaceutically acceptable salt thereof.

11. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chlorophenyl)-4-cyclopropyl-1-(4-methoxybenzyl)-1H-quinazolin-2-one or a pharmaceutically acceptable salt thereof.

12. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chlorophenyl)-4-cyclopropyl-4-methyl-3,4-dihydro-1H-quinazolin-2-one or a pharmaceutically acceptable salt thereof.

13. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chlorophenyl)-4-cyclopropyl-3,4-dimethyl-3,4-dihydro-1H-quinazolin-2-one or a pharmaceutically acceptable salt thereof.

- 90 -

14. A method of Claim 1 in which the antiprogestin compound is 6-(3-Chloro-phenyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one or a pharmaceutically acceptable salt thereof.

15. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate.

16. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

17. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

18. A method of contraception of Claim 17 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

19. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

20. A method of contraception of Claim 19 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to

- 92 -

about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg

b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

21. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

22. A pharmaceutically useful kit adapted for daily oral administration of Claim 21 which comprises:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

23. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

24. A pharmaceutically useful kit adapted for daily oral administration of Claim 23 which comprises:

- a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of three daily dosage units of an antiprogestin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

25. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg

- 94 -

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

26. A pharmaceutically useful kit adapted for daily oral administration of Claim 25 which comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg

b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

INTERNATIONAL SEARCH REPORT

Int'l. Appl. No.
PCT/US 00/11644

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 A61K45/06 A61K31/57 A61P15/18 //((A61K31/57,31:535, 31:565),(A61K31/57,31:495,31:565),(A61K31/57,31:47,31:565)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 696 133 A (HAMANN LAWRENCE G ET AL) 9 December 1997 (1997-12-09) claims 1,4,5 ---	1-26
Y	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8 ---	1-26
Y	WO 96 15794 A (BALANCE PHARMACEUTICALS INC) 30 May 1996 (1996-05-30) page 6, line 15 -page 7, line 23 ---	1-26
Y	WO 97 49407 A (AKZO NOBEL NV ;COELINGH BENNINK HERMAN JAN TI (NL); VERBOST PIETER) 31 December 1997 (1997-12-31) page 2, line 29 -page 3, line 6 ---	1-26 -/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search	Date of mailing of the international search report	
28 August 2000	05/09/2000	
Name and mailing address of the ISA	Authorized officer	
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Bonzano, C	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11644

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 521 166 A (GRUBB GARY S) 28 May 1996 (1996-05-28) claim 1 column 2, line 41 - line 60 -----	1-26
Y	US 5 733 902 A (SCHNEIDER MARTIN) 31 March 1998 (1998-03-31) column 1, line 13 - line 19 -----	1-26
Y	DE 43 44 463 A (SCHERING AG) 29 June 1995 (1995-06-29) page 2, line 1 - line 16 -----	1-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,15-26 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Present claims 1,6-14,16-26 relate to a compound defined by reference to a desirable characteristic or property, namely the activity as progestational.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combinations of the compounds specifically mentioned in example 12, with due regard to the general idea underlying the present invention.

Claims searched completely: none.

Claims searched incompletely: 1-26.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 00/11644

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5696133 A	09-12-1997	AU	717251 B	23-03-2000
		AU	4597796 A	10-07-1996
		BR	9510486 A	02-06-1998
		CA	2208347 A	27-06-1996
		CN	1175247 A	04-03-1998
		CZ	9701761 A	16-09-1998
		EP	0800519 A	15-10-1997
		HU	78117 A	29-11-1999
		JP	10510840 T	20-10-1998
		NO	972591 A	14-08-1997
		WO	9619458 A	27-06-1996
		US	5696130 A	09-12-1997
		US	5688808 A	18-11-1997
		US	5693646 A	02-12-1997
		US	5688810 A	18-11-1997
		US	5693647 A	02-12-1997
		US	5696127 A	09-12-1997
		US	6093821 A	25-07-2000
		US	5994544 A	30-11-1999
DE 4330234 A	09-03-1995	NONE		
WO 9615794 A	30-05-1996	CA	2205897 A	30-05-1996
		EP	0792152 A	03-09-1997
WO 9749407 A	31-12-1997	AU	3436097 A	14-01-1998
		BR	9709934 A	10-08-1999
		CZ	9804289 A	11-08-1999
		EP	0912186 A	06-05-1999
		NO	986104 A	23-12-1998
		NZ	332894 A	28-05-1999
		PL	330916 A	07-06-1999
US 5521166 A	28-05-1996	AU	711179 B	07-10-1999
		AU	4473096 A	10-07-1996
		CA	2208007 A	27-06-1996
		EP	0799043 A	08-10-1997
		JP	10513152 T	15-12-1998
		WO	9619227 A	27-06-1996
US 5733902 A	31-03-1998	DE	3733478 A	13-04-1989
		AT	83149 T	15-12-1992
		AT	106730 T	15-06-1994
		AU	2332188 A	20-04-1989
		AU	2332288 A	08-06-1989
		CA	1330039 A	07-06-1994
		CA	1329126 A	03-05-1994
		DE	3850026 D	06-07-1995
		DE	3876582 A	21-01-1993
		DK	550088 A	02-04-1989
		DK	550188 A	02-04-1989
		EP	0310541 A	05-04-1989
		EP	0310542 A	05-04-1989
		ES	2053795 T	01-08-1994
		ES	2055745 T	01-09-1994
		GR	3007225 T	30-07-1993
		IE	65165 B	04-10-1995
		IE	66335 B	27-12-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No	
PCT/US 00/11644	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5733902 A		IL 87885 A IL 87886 A JP 1106823 A JP 2620333 B JP 1106822 A JP 2656958 B PH 26774 A US 4888331 A ZA 8807378 A ZA 8807379 A	10-06-1993 10-06-1993 24-04-1989 11-06-1997 24-04-1989 24-09-1997 28-09-1992 19-12-1989 30-05-1989 30-05-1989
DE 4344463 A	29-06-1995	WO 9517193 A EP 0735882 A JP 9510183 T	29-06-1995 09-10-1996 14-10-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 November 2000 (09.11.2000)

PCT

(10) International Publication Number
WO 00/66165 A1

(51) International Patent Classification⁷: A61K 45/06,
31/57, A61P 15/18 // (A61K 31/57, 31:535, 31:565)
(A61K 31/57, 31:495, 31:565) (A61K 31/57, 31:47,
31:565)

Diego, CA 92129 (US). JONES, Todd, K. [US/US];
546 Marview Drive, Solana Beach, CA 92075 (US).
TEGLEY, Christopher, M. [US/US]; 478 Thunderhead
Street, Thousand Oaks, CA 91360 (US). ZHANG, Puwen
[CN/US]; 7004 Oriole Court, Audubon, PA 19403 (US).
FENSOME, Andrew [US/US]; 779 Trephanny Lane,
Wayne, PA 19087 (US). TERESENKO, Eugene, A.
[US/US]; 266 Live Oak Drive, Quakertown, PA 18951
(US). WROBEL, Jay, E. [US/US]; 15 Rosetree Lane,
Lawrenceville, NJ 08648 (US). EDWARDS, James, P.
[US/US]; 8723 Hesby Court, San Diego, CA 92129 (US).

(21) International Application Number: PCT/US00/11644

(22) International Filing Date: 1 May 2000 (01.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/183,042 4 May 1999 (04.05.1999) US
09/552,357 19 April 2000 (19.04.2000) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 09/552,357 (CON)
Filed on 19 April 2000 (19.04.2000)

(71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralta Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San

(74) Agents: KODROFF, Cathy, A. et al.; Howson & Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

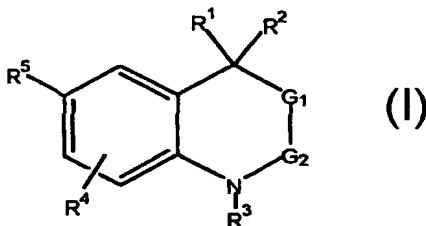
Published:

— with international search report

[Continued on next page]

(54) Title: CONTRACEPTIVE COMPOSITIONS CONTAINING QUINAZOLINONE AND BENZOXAZINE DERIVATIVES

WO 00/66165 A1



O, G₂ is CR₇R₈, and G₁ and G₂ cannot both be CR₇R₈; R₇ and R₈ are H or an optionally substituted alkyl, aryl, or heterocyclic moiety; or pharmaceutically acceptable salt thereof. These methods may be used for contraception or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.

(57) Abstract: This invention relates to cyclic combination therapies utilizing, in combination with progestins, estrogens, or both, compounds which are progesterone receptor antagonists of general structure: (I) wherein: R¹ and R² are H, COR^A, or NR^BCOR^A, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heterocyclic; or R¹ and R² fuse to form 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic rings; R^A is H or optionally substituted alkyl, aryl, alkoxy, or aminoalkyl groups; R^B is H or alkyl; R³ is H, OH, NH₂, COR^C or alkyl, alkenyl, or alkynyl; R^C is H, alkyl, aryl, alkoxy, or aminoalkyl; R⁴ is H, halogen, CN, NO₂, alkyl, alkynyl, alkoxy, amino or aminoalkyl; R⁵ is benzen or 5- or 6-membered heterocyclic ring; R⁶ is H or alkyl; G₁ is O, NR₇, or CR₇R₈; G₂ is CO or CR₇R₈; provided that when G₁ is

WO 00/66165 A1



(48) Date of publication of this corrected version:
22 November 2001

Previous Correction:
see PCT Gazette No. 24/2001 of 14 June 2001, Section II

(15) Information about Corrections:
see PCT Gazette No. 47/2001 of 22 November 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.